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TYPE-SPECIFIC ANTIBODIES IN THE BLOOD OF PATIENTS WITH PNEUMOCOCCIC PNEUMONIA

DETECTION, INCIDENCE, PROGNOSTIC SIGNIFICANCE AND RELATION TO THERAPIES

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Because it was thought that a study of the demonstrable phenomena of immunity of the host which accompany recovery from pneumococcic infections provided an approach to rational therapeutic procedure, such phenomena were the chief concern of investigators prior to the introduction of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). Ever since the drug has been therapeutically employed attention has shifted to the infecting organism and emphasis has been placed on the mechanism of bacteriostasis. At present, attention is again directed to the humoral recovery mechanisms in relation to the action of sulfanilamide and its derivatives. Whitby found that sulfapyridine did not affect the quality, quantity or speed of production of antibodies. It has been observed that many patients who recover from pneumococcic pneumonia under treatment with sulfapyridine do so without any detectable circulating antibodies having developed. Results of adequate investigation of the possible complementary activity of the drug and of the antibody have not been recorded.

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There is still an appreciable mortality in all reported series of cases of pneumococcic pneumonia treated with sulfapyridine alone, although it appears to be less than the mortality previously experienced when treatment was with specific antipneumococcus serum. Whether the residual mortality might be diminished by therapy with a judicious combination of specific serum and sulfapyridine would appear to be answerable only by complete studies on large comparable groups of patients treated with sulfapyridine with and without serum Such groups are not comparable without immunologic studies. During our observations on the antigen-antibody balance of patients with pneumococcic pneumonia who received treatment we compared the antibody response of 135 of them given sulfapyridine, serum or the two combined. Analysis of the results of such therapy forms the basis of the present communication, the incidence and significance of circulating capsular polysaccharide having been separately reported.

MATERIAL AND METHODS

The samples of blood were obtained from the 135 patients by the method indicated in the previous report.[1] Agglutinin and precipitin titers were simultaneously determined in all instances.

Detection of Agglutinin.—Five-tenths cubic centimeter of each of a series of dilutions (from 1:2 to 1:32) of patient's serum in physiologic solution of sodium chloride was mixed with 0.5 cc. of heat-killed pneumococci suspended in a similar solution. The bacterial suspension was freshly prepared by suspending the sediment of an eighteen hour serum-broth culture of a stock strain of pneumococci in physiologic solution of sodium chloride and adjusting the mixture to a ground glass density. The suspended organisms were heat killed (forty-five minutes at a temperature of 56 C.) before use. A positive and a negative control tube were included with each determination.

Detection of Precipitin.—Five-tenths cubic centimeter of each of a series of dilutions (from 1:2 to 1:8) of patient's serum in physiologic solution of sodium chloride was mixed with 0.5 cc. of the "optimal" dilution of a commercial preparation of homologous capsular polysaccharide in a physiologic solution of sodium chloride. A negative control containing 0.5 cc. of a 1:2 dilution of patient's serum and 0.5 cc. of the optimal solution of heterologous capsular polysaccharide was always included.

The determinations of antibodies were made at the same time as those of capsular polysaccharide elsewhere described.[1] In figure 1 of the preceding report a schematic representation of the method was given. All determinations were carried out in 10 by 75 mm. pyrex agglutination tubes and included centrifugation for thirty minutes at 2,000 revolutions per minute.

RESULTS

Treatment with Sulfapyridine Alone.—Sixty-five of the 135 patients in this series were treated with sulfapyridine alone. Generally an initial

1. Bukantz, S. C.; de Gara, P. F., and Bullowa, J. G. M.: Capsular Polysaccharide in the Blood of Patients with Pneumococcic Pneumonia: Detection, Incidence, Prognostic Significance and Relation to Therapies, Arch. Int. Med., February 1942.

oral dose of 5 Gm. was followed by a dose of 1 Gm. every four hours; occasionally supplementary intravenous injections of the sodium salt of the drug were given. The level of sulfapyridine in the blood was of the usual magnitude (2 to 8 mg. per hundred cubic centimeters).

A total of 350 specimens of blood were analyzed for antibodies (agglutinins and precipitins) during observation of the 65 patients treated with sulfapyridine alone. The 25 patients with type III pneumococcus pneumonia were studied most intensely and for each of 4 of them as many as 11 to 21 determinations were made.

TABLE 1.—*Incidence of Antibodies in Sixty-Five Sulfapyridine-Treated Patients with Pneumococcic Pneumonia*

	Number of Patients	Percentage of Patients
Total	65	100.0
Antibodies present	45	69.2
Agglutinins only	23	35.4
Agglutinins and precipitins	22	33.8
Precipitins only	0	0.0
No antibodies	20	30.7

TABLE 2.—*Day of Disease on Which Antibodies First Appeared in Forty-Five Sulfapyridine-Treated Patients with Pneumococcic Pneumonia*

Day of Disease	Number of Patients	Percentage of Patients		Number of Deaths
1 and 2	0	0		0
3	2	4.5		0
4	1	2.2		0
5	1	2.2		0
6	3	6.7		0
7	2	4.5		0
8	8	17.8		0
9	11	24.4	80	1
10+	17	37.8		2
Total	45	100.0		3

As recorded in table 1, either agglutinins or agglutinins and precipitins developed in 45, or 69.2 per cent, of the 65 patients at some time during the course of their illness. Precipitins were detected in approximately 50 per cent (22 to 45) of the patients in whom antibodies developed.

Table 2 gives the day of disease on which antibodies were first detected in the 45 patients. In 36, or 80 per cent, of them antibodies appeared first on or after the eighth day of disease. This observation is in agreement with those of Finland, Spring and Lowell [2] and of

2. Finland, M.; Spring, W. C., Jr., and Lowell, F. C.: Immunological Studies on Patients with Pneumococcic Pneumonia Treated with Sulfapyridine, J. Clin. Investigation **19**:179, 1940.

Kneeland and Mulliken.[3] It will be noted from table 1 that both agglutinins and precipitins developed in 22 patients.

In 13 of them the agglutinin and the precipitin reactions became positive on the same day of disease, while in 8 a positive agglutinin reaction was obtained some time before the precipitin was detected; in 5 of these 8 patients the agglutinin reaction was positive four or more days earlier. In 1 patient with pneumonia caused by a type VII pneumococcus the precipitin reaction was repeatedly positive for eleven days before an agglutinin reaction was obtained. Subsequently, however, in

TABLE 3.—*Relation of Type of Causative Pneumococcus, Occurrence of Bacteremia, Age of Patient, Development of Antibodies and Outcome of Illness in Sixty-Five Sulfapyridine-Treated Patients with Pneumococcic Pneumonia*

	All Ages				40 Years or Less				40 Years or More			
	Total Number		Number with Antibodies		Total Number		Number with Antibodies		Total Number		Number with Antibodies	
Type	Patients	Deaths	Patients	Deaths	Patients	Deaths	Patients	Deaths	Patients	Deaths	Patients	Deaths
I	11 2*	1 0*	8 1*	0 0*	8 1*	0 0*	6 0*	0 0*	3 1*	1 0*	2 1*	0 0*
II	1 0*	0	1 0*	0	0		0		1 0*	0	1 0*	0
III	25 5*	4 2*	14 2*	1 1*	6 0*	0	4 0*	0	19 5*	4 2*	10 2*	1 1*
V	5 2*	1 1*	2 1*	1 1*	4 1*	1 1*	2 1*	1 1*	1 1*	0 0*	0	
VII	16 4*	1 1*	15 4*	1 1*	8 1*	0 0*	7 1*	0 0*	8 3*	1 1*	8 3*	1 1*
VIII	7 1*	1 1*	5 0*	0	3 0*	0	3 0*	0	4 1*	1 1*	2 0*	0
Total	65 14*	8 5*	45 8*	3 3*	29 3*	1 1*	22 2*	1 1*	36 11*	7 4*	23 6*	2 2*

* Bacteremia.

the same patient the precipitin reaction became negative, while the agglutinin titer rose and persisted at a high level for at least thirteen days.

Table 3 gives the antibody response in relation to the type of infecting pneumococcus, age, presence of bacteremia, detectability of capsular polysaccharide and outcome for all 65 patients. Although the group is too small to permit generalization, there appears to be a tendency to a lower incidence of detectable antibodies among patients with type III pneumococcus pneumonia than among those whose pneumonia is caused by Pneumococcus type I, VII or VIII.

3. Kneeland, Y., Jr., and Mulliken, B.: Antibody Formation in Cases of Lobar Pneumonia Treated with Sulfapyridine, J. Clin. Investigation **19**:307, 1940.

Twenty-nine of the 65 patients were under 40 years of age; in 22 of them antibodies developed (76 per cent) (tables 3 and 4). Thirty-six patients were more than 40 years of age; in 23 of them (64 per cent) antibodies developed. Fifty-seven of the 65 sulfapyridine-treated patients recovered. In 15 of the 57 antibodies were not detected at any time. Of the 8 patients who died 1 each had pneumonia caused by

TABLE 4.—*Age of Patient and Outcome of Illness in Relation to Development of Antibodies in Sixty-Five Sulfapyridine-Treated Patients with Pneumococcic Pneumonia* *

Age	Total Number			Number with Agglutinins			Number with Agglutinins and Precipitins			Number Without Antibodies		
	Patients	Deaths		Patients	Deaths		Patients	Deaths		Patients	Deaths	
		No.	%		No.	%		No.	%		No.	%
Under 40 years	29	1	3.4	14	1	7.1	8	0	0.0	7	0	0.0
Over 40 years	36	7	19.5	9	2	22.2	14	0	0.0	13	5	38.4
Total	65	8	12.3	23	3	13.1	22	0	0.0	20	5	25.0

* No significant differences in chi square exist between the mortality rates in the different groups.

TABLE 5.—*Relation of Occurrence of Bacteremia, Production of Capsular Polysaccharide, Development of Antibodies and Outcome of Illness in Sixty-Five Sulfapyridine-Treated Patients with Pneumococcic Pneumonia*

	Bacteremia Absent		Bacteremia Present		Total	
	Number of Patients	Number with Antibodies	Number of Patients	Number with Antibodies	Number of Patients	Number with Antibodies
Capsular polysaccharide present						
Patients	3	0	7	3	10	3
Deaths	2	0	4	2	6	2
Capsular polysaccharide absent						
Patients	48	37	7	5	55	42
Deaths	1	0	1	1	2	1
Total						
Patients	51	37	14	8	65	45
Deaths	3	0	5	3	8	3

pneumococcus type I, V, VII or VIII and in 4 the infecting pneumococcus was type III. Seven of the 8 patients were over 40 years of age; in 5 of them no antibodies were detected. In the remaining 3 patients who died only an agglutinin reaction was obtained. There were no deaths among the 22 patients who gave positive reactions for both precipitins and agglutinins.

Table 5 relates the incidence of bacteremia, the development of antibodies, the occurrence of capsular polysaccharide and the outcome of illness in the patients treated with sulfapyridine alone. It will be noted that of the 51 nonbacteremic patients, antibodies developed in 37

(72.5 per cent), in none of 3 who gave positive reactions for capsular polysaccharide and in 37 of 48 with negative reactions for that substance. In only 3 of 7 bacteremic patients were antibodies and polysaccharide present simultaneously, while antibodies developed in 5 of 7 bacteremic patients with negative reactions for the polysaccharide. Agglutinins only were detectable in 3 of a total of 10 patients with positive reactions for capsular polysaccharide, whereas either agglutinins alone or both agglutinins and precipitins developed in 42 of 55 patients who gave negative reactions for that substance. No deaths occurred among the 37 nonbacteremic patients with a negative reaction for capsular polysac-

TABLE 6.—*Highest Agglutinin and Precipitin Titers Observed Among Forty-Five Sulfapyridine-Treated Patients with Pneumococcic Pneumonia (Forty-Two Recoveries; Three Deaths)* *

		Agglutinin		Precipitin		
		Dilution of Patient's Serum				
	Total	1:16 or Less	1:32 or 1:64	¼	1/16	1/16
		No. of Patients		No. of Patients		
Bacteremia and capsular polysaccharide absent	16†	13	3	0	0	0
	21‡	4	17	4	7	10
Bacteremia and capsular polysaccharide present	3	2 (1)§	1 (1)#	0	0	0
Bacteremia present and capsular polysaccharide absent	4†	3 (1)	1	0	0	0
	1‡	1	0	1	0	0
Total	45	23	22	5	7	10

* All patients in whom antibodies developed before the eighth day of illness recovered.
† Agglutinin only.
‡ Both agglutinin and precipitin.
§ The figure in parentheses indicate the number of deaths in the group.
# The case of this patient is described in the text and in a previous paper.[1]

charide in whom antibodies developed, but there were 3 deaths among 14 such patients in whom antibodies failed to develop. Among the bacteremic patients, 3 of the 8 with antibodies and 2 of the 6 without antibodies died. Among the 7 bacteremic patients with positive reactions for capsular polysaccharide, 2 of the 3 in whom antibodies developed died and 2 of the 4 in whom antibodies did not develop died. The 3 remaining patients with such reactions were all nonbacteremic, and none showed antibodies; 2 of them died. Antibodies developed in 5 of 7 bacteremic patients whose reaction for the polysaccharide was negative, and 1 of the 5 died.

From table 6 it will be noted that only agglutinins developed in 16 nonbacteremic patients with a negative reaction for capsular polysaccharide; in 13 of them the agglutinin titer ranged between 1 : 4 and 1 : 16. In 21 such patients both agglutinins and precipitins developed, and in 17 the agglutinin titer was 1 : 32 or greater. As just noted, none of

these patients died. Of 5 patients whose agglutinin titer was 1:32 or more but in whom precipitins did not develop, 1 died. This patient was a 54 year old diabetic woman with bacteremia and a positive reaction for capsular polysaccharide who was admitted to the hospital late in the course of her illness with evidences of accumulation of fluid in the pleural cavity; her blood was examined on only one occasion. Her death was at least partly determined by the severity of the diabetes, the presence of capsular polysaccharide and apparently a too early cessation of treatment with sulfapyridine. Three recoveries occurred among 5 bacteremic patients (2 with positive and 3 with negative reactions for capsular polysaccharide) in whom precipitins failed to develop and whose agglutinin titer was 1:16 or less. Recovery occurred in all 13 non-bacteremic patients in whom the agglutinin titer was 1:16 or less and yet in whom no precipitins were detectable.

TABLE 7.—*Distribution of Positive Antibody Responses and Outcome of Illness in Relation to Day of Disease on Which Sulfapyridine Therapy Was Begun in Sixty-Five Patients with Pneumococcic Pneumonia Treated with Sulfapyridine Alone*

Day of Disease	Total			Number of Patients with Antibodies
	Patients	Deaths		
		Number	Percentage	
First to fourth	26	3	11.6	18
Later than fourth	39	5	12.8	27

Table 7 shows the relation between the day of disease on which treatment with sulfapyridine alone was begun, the antibody response and the outcome of the disease. Sixty per cent of the 65 patients given only sulfapyridine were first treated on or after the fifth day, and the percentage of positive antibody responses and the mortality rate were identical for those treated "early" and for those treated "late."

Treatment with Specific Antipneumococcus Serum Alone.—Thirty-one patients were treated with varying amounts of specific antipneumococcus serum (horse or rabbit) alone. Antibodies were detected in the blood of all 31 and always were found in the first sample of blood tested after therapy was begun. Agglutinins and precipitins were present in 27 patients, of whom 2 died. In 3 patients agglutinins only were detected and these in relatively low titer, 1:8; all 3 recovered. In the remaining patient on the eleventh day of a type IV pneumococcus pneumonia which had been treated on the second day precipitins only were detected; the illness terminated in subacute bacterial endocarditis due to the same organism.

The total dose of serum administered ranged from 85,000 to 1,239,000 U. S. P. units. The antibody titers reached were appreciably higher for these patients than for those treated with sulfapyridine alone. In 24 of the 30 patients in whom agglutinin was present the titer was 1:32 or greater, in 3 it was 1:16 and in the remaining 3 it was 1:8. Of the 28 patients with a positive precipitin reaction, the titer was 1:8 or greater in 25 (greater than 1:16 in 8) and 1:4 in the remaining 3. Table 8 summarizes by type of causative pneumococcus the relation between age and outcome in this group of patients. Those with type III

TABLE 8.—*Relation of Type of Causative Pneumococcus, Incidence of Bacteremia, Age of Patient, Presence of Capsular Polysaccharide and Outcome of Illness in Thirty-One Patients with Pneumococcic Pneumonia Treated with Antipneumococcus Serum Alone*

	All Ages		40 Years or Less		40 Years or Over	
Type	Patients	Deaths	Patients	Deaths	Patients	Deaths
I	11	0	9	0	2	0
	2*	0*	1*	0*	1*	0*
II	1	0	0	..	1	0
	1*	0*			1*	0*
III	2 (1)†	2 (1)	1 (1)	1 (1)	1	1
	0*	0*	0*	..	0*	..
IV	1	1	0	..	1	1
	1*	1*			1*	1*
V	2	0	2	0	0	..
	1*	0*	1*	0*		
VII	9	0	5	0	4	0
	4*	0*	2*	0*	2*	0*
VIII	5	0	4	0	1	0
	1*	0*	1*	0*	0*	
Total	31 (1)	3 (1)	21 (1)	1 (1)	10	2
	10*	1*	5*	0*	5*	1*

* Bacteremia.

† The figure in parentheses indicates the number of patients in whose blood capsular polysaccharide was detectable.

pneumococcus pneumonia were usually alternated for treatment with sulfapyridine alone and with specific serum combined with sulfapyridine, which accounts for the fact that so few (2) patients received only serum.

Treatment with Sulfapyridine and Specific Antipneumococcus Serum.—Thirty-nine patients were treated with both specific antipneumococcus serum and sulfapyridine. Antibodies were not detected in 3 of them. These were 3 of the 13 patients with type III pneumococcus pneumonia who were thus treated; all 3 were nonbacteremic, and their blood gave a negative reaction for capsular polysaccharide; all of them recovered. In 6 patients only agglutinins were detected (1 case each of types II, III, V and VIII pneumococcus pneumonia and 2 cases of type I pneumococcus pneumonia); in 3 of these the titer was 1:16 or less, and in the

remaining 3, 1:32 or greater. These 6 patients also recovered. In 27 patients both agglutinins and precipitins were detected. The agglutinin titer was 1:16 or less in 8 patients and 1:32 or greater in 19, while the precipitin titer was 1:4 in 7 and 1:8 or greater in 20 (13 gave a 1:16 titer). Five of these patients died; in 3 of the 5 the agglutinin titer was greater than 1:32 and the precipitin titer greater than 1:8. There were neither complications of the pneumonia nor evidence of other significant disease in these patients. In 3 of them capsular polysaccharide was found; their cases are described in the preceding paper (cases 5, 8

TABLE 9.—*Relation of Type of Causative Pneumococcus, Incidence of Bacteremia, Age of Patient, Presence of Capsular Polysaccharide and Outcome of Illness in Thirty-Nine Patients with Pneumococcic Pneumonia Treated with Both Sulfapyridine and Antipneumococcus Serum*

Type	All Ages		40 Years or Less		40 Years or Over	
	Patients	Deaths	Patients	Deaths	Patients	Deaths
I	10	0	5	0	5	0
	1*	0*	1*	0*	0*	
II	2	0	1	0	1	0
	1*	0*	1*	0*	0*	
III	13 (2)†	2 (2)	5	0	8 (2)	2 (2)
	2*(1)	1*(1)	1*	0*	1*(1)	1*(1)
V	2	1	1	1	1	0
	0*	..	0*	..	0*	
VII	8 (2)	2 (1)	4	0	4 (2)	2 (1)
	2*(1)	2*(1)	0*	..	2*(1)	2*(1)
VIII	4 (1)	0	1	0	3 (1)	0
	1*(1)	0*	0*		1*(1)	0*
Total	39 (5)	5 (3)	17	1	22 (5)	4 (3)
	7*(3)	3*(2)	3*	0*	4*(3)	3*(2)

* Bacteremia.

† The figure in parentheses indicates the number of patients in whose blood capsular polysaccharide was detectable.

and 14).[1] In 1 of them moderate leukopenia developed during the course of treatment but subsided promptly after therapy with sulfapyridine was stopped (case 5). To 1 of the other patients antipneumococcus serum (type V) was given on the fifth day of illness and sulfapyridine on the sixth day, and to the remaining 1 patient serum (type VII) and sulfapyridine were given on the twelfth day. In the case of the last 2 patients complete antibody studies were not possible. Table 9 summarizes the incidence of the various types of pneumococcic pneumonia and the relation between age and outcome in patients treated with both serum and sulfapyridine.

The total dose of serum administered to these patients ranged from 12,500 to 2,525,000 U. S. P. units. There was no significant difference in the antibody titers developed in the patients receiving serum alone

and those in patients given serum and sulfapyridine simultaneously. In some instances high titers were obtained despite administration of relatively small quantities of serum, while administration of larger

TABLE 10.—*Relation of Antibody Response, Day of Disease on Which Therapy Began, Amount of Antipneumococcus Serum Administered and Type of Causative Pneumococcus in Thirty-Four Patients with Pneumococcic Pneumonia Treated with Serum Alone*

Case No.	Type of Pneumococcus	Units (U. S. P.) of Serum	Day of Disease Serum Therapy Began	Highest Titers: Agglutinins 4	8	16	32	64+	Precipitins 4	8	16+
1	II	1,239,000	8	..	..	..	1	..	..	..	1
2	I*	525,000	5	..	..	..	..	1	..	..	1
3	I	280,250	2	..	..	..	..	1	..	..	1
4	I	210,000	4	..	..	1	..	..	1	..	..
5	I	160,000	7	..	..	..	..	1	..	..	1
6	I	165,000	2	..	1	..	..	..	0	0	0
7	III*	700,000	1	..	..	1	..	..	1	..	..
8	III	260,000	?	..	..	..	..	1	..	..	1
9	IV*	733,000	4	0	0	0	0	0	..	..	1
10	V*	634,000	6	..	..	..	..	1	..	..	1
11	V	140,000	5	..	..	..	1	..	..	1	..
12	VII	320,000	2	..	..	..	..	1	..	..	1
13	VII*	640,000	7	..	..	..	..	1	..	..	1
14	VII	229,000	4	..	1	..	..	..	0	0	0
15	VIII	85,000	4	..	1	..	..	..	0	0	0
16	VIII*	285,000	5	..	..	..	..	1	..	..	1
17	VIII	184,000	3	..	..	..	1	..	..	..	1
18	I*	235,000	3	..	..	..	1	..	0	0	0
19	I	12,500	5	1	..	..	..	..	0	0	0
20	I	98,000	4	..	..	..	..	1	..	..	1
21	II	120,000	4	..	..	1	..	..	0	0	0
22	III	123,500	7	..	1	..	..	..	0	0	0
23	III	84,500	5	..	..	..	..	1	..	..	1
24	III	170,000	2	0	0	0	0	0	0	0	0
25	III	300,000	2	0	0	0	0	0	0	0	0
26	III	200,000	2	0	0	0	0	0	0	0	0
27	III*	495,000	12	..	..	1	..	..	..	1	..
28	V	273,000	5	1	..	..	..	..	1	..	..
29	V	200,000	8	..	..	..	1	..	0	0	0
30	VII*	2,525,000	2	..	..	..	1	..	..	1	..
31	VII*	160,000	12	..	..	..	..	1	..	..	1
32	VII	192,000	5	..	..	..	..	1	..	1	..
33	VIII*	180,000	1	..	..	..	..	1	..	..	1
34	VIII	132,000	3	..	..	..	..	1	0	0	0

No antibodies	3
Agglutinins only	9
Precipitins only	1
Agglutinins and precipitins	21

* Bacteremia.

quantities did not always result in high antibody titers. As has just been noted, the development of a high titer of antibody was not always followed by recovery. The relation of antibody response to the quantity of serum administered, with the type of infecting pneumococcus and the day of disease on which administration of serum was begun, is given in table 10 for some of the patients.

COMMENT

Detectable antibodies developed during recovery in a high percentage (70) of the patients treated with sulfapyridine alone, though they appeared in the majority some days after the disease seemed to be under clinical control. These observations are in agreement with those of Finland, Spring and Lowell,[2] who found that antibodies developed in sulfapyridine-treated patients with about the same frequency as in untreated patients. Kneeland and Mulliken,[3] however, found a considerably lower incidence of antibody response among sulfapyridine-treated patients with lobar pneumonia (4 of 19) and suggested that the low rate of and delay in antibody formation might be a consequence of lessened stimulus resulting from the action of the drug on the invading organism. Kneeland and Mulliken performed only the precipitin test on the assumption that agglutinins, precipitins and protective antibodies are the same and therefore are detectable with equal ease. While the various phenomena of immunity may be manifestations of a single antibody, the physical conditions required for qualitative detection are quite different. This difference is indicated by the detectability of protective antibodies earlier than agglutinins in an appreciable percentage of the cases reported by Finland and his associates [2] and the detectability of agglutinins without precipitins in a large number of our sulfapyridine-treated patients. Tillett and Francis [4] stated that "type specific antibodies were more easily demonstrable by agglutination tests with the intact type specific cells," although in most of their 19 horse-serum–treated patients agglutinins and precipitins became detectable at the same time.

Of the 45 patients in our sulfapyridine-treated group in whom antibodies developed, 3 died and 42, or 93.4 per cent, recovered. Of the 20 sulfapyridine-treated patients in whom antibodies failed to develop, 5 died and 15, or 75 per cent, recovered. Apparently, though not all the sulfapyridine-treated patients die if antibodies fail to develop, the appearance of antibodies is not always followed by recovery.[5] The fatality rate among patients in whom antibodies developed was only one quarter of the rate among those in whom they failed to develop. For this reason it is important to determine the factors involved in the production of antibodies.

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4. Tillett, W. S., and Francis, T., Jr.: Cutaneous Reactions to Polysaccharides and Proteins of the Pneumococcus in Lobar Pneumonia, J. Exper. Med. **50**: 687, 1929.

5. While this paper was in press, a study by E. C. Curnen and C. M. MacLeod (The Effect of Sulfapyridine upon the Development of Immunity to Pneumococcus in Rabbits, J. Exper. Med. **75**:77, 1942) appeared. Their data support the view that effective therapy of pneumococcic infections in man with sulfanilamide compounds is associated with the development of active immunity.

The rate of production of antibodies was least among those patients in whom capsular polysaccharide was detected, and it is to be expected that production will be lowest among patients whose infection is due to a type of pneumococcus which produces large amounts of capsular polysaccharide. This is particularly important in infections caused by Pneumococcus type III. The appearance of capsular polysaccharide in infection caused by any type of pneumococcus is conditioned by the duration of the disease before successful therapy is begun. In our series, the incidence of patients with a positive reaction for capsular polysaccharide was equal among those treated before and those treated after the fourth day of illness. However, the great majority of patients in the earlier treated series entered the hospital on either the third or the fourth day of their disease and, in effect, created a series almost entirely composed of late treated patients. It is probable that the incidence of capsular polysaccharide would be considerably lower in a series of patients treated early in their disease. And in such patients we should expect to find an even higher incidence of antibody response. Likewise, a low antibody response was observed among older patients and among those with bacteremia.

Because fatality rates of sulfapyridine-treated patients are greater when antibodies fail to appear, we believe it advisable to administer specific serum to those patients in whom a failure of antibody formation is most likely to occur, i. e., those with infections caused by Pneumococcus type III, those with bacteremia or a positive reaction for capsular polysaccharide, those over 40 and those treated late in the course of their disease.

The effort to analyze the deaths among serum-treated patients in terms of quantitative antibody response met with little success. In our relatively small group of patients treated with both sulfapyridine and serum fatalities occurred despite attainment of a high antibody titer. In contrast to this is the observation that of the sulfapyridine-treated patients, there was uniform recovery among those in whom the greatest antibody response developed (i. e., precipitins as well as agglutinins). When antibodies develop spontaneously, as in sulfapyridine-treated patients, such antibodies are immunologically uniform with the stimulating antigen, i. e., the invading organism with its particular capsular polysaccharide. Either other responses (cellular) have been stimulated during the production of antibodies or the passively introduced antibody may imperfectly fit the antigen, and this may account for the discrepancy in outcome of illness in drug-treated and in serum-treated patients having a high antibody titer. It is evident that information concerning the quantitative and the qualitative significance of the antibodies in serum-treated patients is at present inadequate.

SUMMARY

Repeated agglutinin and precipitin determinations were made on 135 patients with type I, II, III, IV, V, VII or VIII pneumococcus pneumonia during the course of treatment with sulfapyridine or specific serum or the two in combination.

Sixty-five patients received sulfapyridine alone; antibodies developed in 45 of them. Agglutinins alone were found in 23 patients; agglutinins and precipitins, in 22. Five of the 20 patients without antibodies died, a mortality rate of 25 per cent. It is apparent that the development of a positive antibody response is associated with a higher recovery rate. Of the 27 patients with the greatest amount of spontaneously produced antibody per unit volume of blood (i. e., agglutinin titer of 1:32 or greater and/or circulating precipitin) only 1, or 3.7 per cent, died. Of the patients having agglutinins of low titer and no precipitins 2 died. Finally, 22 of the 27 patients gave a reaction for both precipitins and agglutinins. None of them died.

In 36 (80 per cent) of the 45 patients in whom antibodies developed, they were first detected on the eighth day of disease or later.

The incidence of detectable antibodies was slightly lower among patients with type III pneumococcus pneumonia than among those whose infection was caused by Pneumococcus type I, VII or VIII. The antibody response was definitely lower in patients over 40.

The incidence of positive antibody response was slightly higher in the nonbacteremic than in the bacteremic patients. The lowest incidence of positive antibody responses occurred among the 10 patients with a positive reaction for capsular polysaccharide; antibodies (agglutinins only) developed in only 3 of the 10.

The incidence of positive antibody response and mortality rate was unchanged whether patients were treated in the early stages of the disease or in the late stages. However, in the case of the average early treated patient therapy was begun on the third or fourth day of disease.

Thirty-one patients were treated with specific antipneumococcus serum alone; antibodies were detected in all of them in the first sample of blood obtained after therapy was begun. Three of them died.

Thirty-nine patients received both specific serum and sulfapyridine. Antibodies failed to develop in 3 of them, all with infection caused by type III Pneumococcus and none with bacteremia, despite administration of 170 to 300,000 units of serum. All 3 patients, however, recovered. Among 27 of the 39 patients who gave positive precipitin and agglutinin reactions, 5 deaths occurred. Four of the patients who died had either bacteremia or a positive reaction for capsular polysaccharide or both. The fifth patient had neither bacteremia nor a positive reaction for capsular polysaccharide and had only low agglutinin and precipitin titers.

No constant relation was observed between the amount of serum administered and the height of the antibody response either in the patients treated with serum alone or in those treated with serum and sulfapyridine in combination.

It is suggested that specific serum therapy be employed with sulfapyridine therapy whenever there are circumstances which may impede the spontaneous production of antibody, i. e., age over 40 years, presence of bacteremia or circulating capsular polysaccharide or presence of infection caused by Pneumococcus type III.

Miss Ruth Mayer assisted in titrations of capsular polysaccharide and of antibodies on most of the patients.

Miss Constance Lebair and Miss Evelyn Greenbaum assisted in the preparation of the manuscript.

EFFECT OF ESTROGEN ON THE UTILIZATION OF THE VITAMIN B COMPLEX

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In previously recorded clinical observations [1] we have reported evidence indicating an interrelation between hormones of the anterior lobe of the pituitary and the utilization of the vitamin B complex. In a number of instances, pellagra refractive to vitamin therapy was cured or improved by the parenteral administration of the whole extract of the anterior lobe of the pituitary or of an anterior pituitary extract containing the growth-stimulating or gonadotropic factor.[2] The evaluation of the effects of the growth-stimulating or gonadotropic substance is somewhat vitiated by the inability to exclude the possibility that other factors are present in the solutions administered. The possible effect of any vitamin B complex in these extracts is remote when considered in relation to the amounts of vitamin B complex previously administered.

The effect of the anterior lobe of the pituitary on the utilization of the vitamin B complex may be the result of the action of (*a*) one or more of the known hormones, (*b*) another gland of internal secretion as influenced by a pituitary hormone or (*c*) a pituitary hormone as yet unknown.

One approach to the problem is to ascertain the effects of various glandular substances on vitamin B complex deficiency. For example, Sydenstricker [3] has observed the healing of "lesions of ariboflavinosis"

This work has been greatly aided through a grant from a fund in memory of Miss M. M. Capper.

From the Departments of Medicine and Physiology, Northwestern University Medical School, and the Robert Bruce Preble Laboratory of the Cook County Hospital.

1. (*a*) Sutton, D. C., and Ashworth, J.: Cachexia Responding to Extract of the Anterior Lobe of the Pituitary Gland, J. Lab. & Clin. Med. **25**:848, 1940; (*b*) The Interrelation Between the Vitamin B Complex and the Anterior Lobe of the Pituitary Gland, ibid. **25**:1188-1192, 1940; (*c*) in Harris, S., and Harris, S., Jr.: Clinical Pellagra, St. Louis, C. V. Mosby Company, 1940, sect. 4, chap. 17. (*d*) Sutton, D. C.: Interrelation Between Vitamin B Complex and the Anterior Lobe of the Pituitary Gland, South. M. J. **34**:47-51, 1940.

2. The extracts of the anterior lobe of the pituitary were furnished by Armour and Company, Chicago.

3. Sydenstricker, V. P.: Personal communication to the authors.

after the administration of desoxycorticosterone to a patient with Addison's disease.

This paper records the observations made on the effect of estrogens on patients who, because of chronic alcoholism, evidence of hepatic cirrhosis or slight lesions of the skin, mucous membrane or the nervous system, were classified by us as having subclinical pellagra.

Diethylstilbestrol was used at the beginning of the study; it was later replaced by α-estradiol dipropionate [4] because the latter is considered to be a natural estrogen in contradistinction to the synthetic substance diethylstilbestrol. Permission for this type of management was obtained from each patient. The effects of these estrogens on the utilization of the vitamin B complex, or rather on the condition of the patient, is best illustrated by the following case reports. All patients received the general full diet of the hospital, which is known to be adequate in regard to essential food factors.

REPORT OF CASES

CASE 1.—J. C., a 48 year old white man, entered the Cook County Hospital on Dec. 13, 1940, complaining of diarrhea, cutaneous rash and precordial pain of three weeks' duration. He had been chronically addicted to alcohol for many years, drinking an average of 1 quart (946 cc.) of whisky daily. During November he had had a severe infection of the upper respiratory tract, accompanied by diarrhea, with fifteen to twenty stools daily. On entrance he still was having five to six stools daily. Neither blood nor amebas were found in the feces. Shortly after the onset of diarrhea the patient had noticed a generalized rash, which caused some pruritis. The day before entering the hospital he experienced severe "shooting" pains in the arms and legs. He had had several similar attacks on previous occasions.

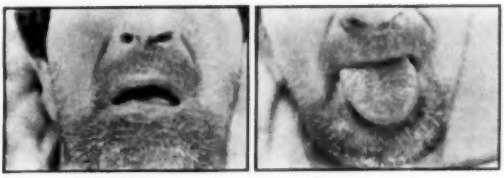
Physical examination revealed nothing abnormal except a maculopapular rash on the forearms and the anterior surface of the body.

The patient was allowed a full diet. From December 13 to December 27 he was given daily 25 mg. of thiamine hydrochloride intravenously and 450 mg. of nicotinic acid orally.

The rash disappeared, and the peripheral pains were much improved. Slight scaling of the dorsum of the hands (pellagrous?) remained.

After medication with thiamine was stopped, on December 28, the patient was given 3 mg. of diethylstilbestrol daily until Feb. 6, 1941. On January 9 the cutaneous lesions on the anterior surfaces of the legs were exacerbated. On January 13 and 19 he was given 200 cc. of a 50 per cent solution of dextrose intravenously. No fever occurred. These injections were followed by a marked exacerbation of the cutaneous lesions, such as occurs in a case of pellagra after the intravenous administration of a solution of dextrose. At this time definite scaling at the angles of the mouth was observed, and the patient mentioned tenderness of the nasal mucosa. On February 4 he complained of an infection of the upper respiratory tract, with acute rhinitis and bronchitis. The pain in the legs became so severe that he was confined to bed. The diethylstilbestrol was discontinued

4. Alpha-estradiol dipropionate (di-ovocylin) was furnished by the Ciba Pharmaceutical Products, Inc., Summit, N. J.



Case 1, Feb. 10, 1941. Note the red tongue and the scaling lesions at the corners of the mouth and along the lips and nose.

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February 6, and instead 1 mg. of α-estradiol dipropionate was given intramuscularly on each of the four succeeding days.

During the night of February 10 the patient was found on the hospital grounds, clad only in a short nightshirt. When examined the next day, he exhibited a severe psychosis. The marked scaling around the lips, especially at the angles of the mouth, extended up on the nasal septum. Similiar scaling was also present in the scrotal thigh folds. The tongue was fiery red. Red, painful, nonpitting edema of both hands completed the picture of pellagra without diarrhea. The daily administration of 100 mg. of nicotinic acid intravenously and 450 mg. orally and 8 cc. of liver extract [4a] intramuscularly caused rapid improvement.

This patient had definite, though mild, pellagra when he entered the ward and had had previous attacks due to vitamin B complex deficiency, as evidenced by attacks of peripheral pain (peripheral neuritis). He was given dextrose intravenously on January 13 and 19 because we believe that the acute exacerbation which follows its use in cases of pellagra serves to confirm the diagnosis of the condition. The extreme severity of the symptoms by February 10 would appear to be the result of the infection of the upper respiratory tract which began February 4. We have frequently noted the onset of pellagra or neuritis in persons chronically addicted to alcohol shortly after an infection of the upper respiratory tract.

Case 2.—W. C., a 44 year old white man, was first seen in January 1939 by one of us (J. A.). He was chronically addicted to alcohol. In October 1938 he was told by his physician that he had cirrhosis of the liver. He stopped drinking and continued on a high carbohydrate diet as ordered. He enjoyed relatively good health until the Christmas holidays of 1939, when he drank heavily of sherry wine (but no distilled spirits) for several days.

When first seen the patient was acutely ill, with a temperature of 103.6 F., jaundice and marked ascites, which was relieved by paracentesis. After this episode of acute illness, severe, painful glossitis developed, which was relieved by frequent intramuscular injections of liver extract from January to September 1940.

After the administration of liver extract was stopped in September, the patient was given 6 mg. of stilbestrol orally for three successive days. On the fourth day he complained of severe glossitis and a painful nasal mucosa. Severe, scaly, seborrhoid lesions about the lips and nose and painful fissures in the angles of the mouth were observed. These lesions were relieved within ten days by the daily administration of 300 mg. of nicotinic acid orally and 4 cc. of liver extract intramuscularly. The patient died in November 1940 of a ruptured esophageal varix, after thirty-two paracenteses.

This man with severe hepatic damage had a type of glossitis frequently seen in cases of pellagra refractory to vitamin therapy, which is usually controlled by the parenteral administration of liver extract.

4a. A crude aqueous extract from which the coagulable protein had been removed by heat was used. One cubic centimeter of this extract, which was prepared by the Armour and Company research laboratories, is equal to 12.5 Gm. of fresh liver.

During liver therapy there were intervals of ten days without treatment before the return of mild symptoms. After a dose of 24 mg. of diethylstilbestrol, severe glossitis developed and cheilosis of the mouth and nose appeared for the first time.

CASE 3.—E. S., a 49 year old white man, entered the Cook County Hospital Dec. 12, 1940, complaining of dyspnea of a year's duration, associated with occasional edema of the ankles, and severe pains in the legs and diarrhea, with twenty to twenty-four watery stools daily, of a week's duration. He was a bartender by occupation and had been a heavy drinker for many years.

He was well nourished and had a blood pressure of 160 systolic and 80 diastolic and slight icterus. The liver and spleen were palpable and firm; more than moderate ascites was present. A diagnosis of alcoholic cirrhosis of the liver was made.

From Dec. 12, 1940, to Jan. 11, 1941 50 mg. of thiamine hydrochloride was given intravenously each day; this therapy was followed by almost complete recovery from polyneuritis. From January 11 until February 4 3 mg. of diethylstilbestrol was given orally each day. Beginning February 6, 1 mg. of α-estradiol dipropionate was administered daily until February 10, when the dose was increased to 5 mg. daily. The administration of the thiamine hydrochloride was continued throughout. Slight scaling of the corners of the mouth was noticed a week after the administration of diethylstilbestrol. The nasal mucosa became painful, and numbness and paresthesias developed in the hands. The pains in the legs became less severe.

This patient also was chronically addicted to alcohol, with a damaged, cirrhotic liver. The only evidence of avitaminosis manifested on entrance to the hospital was polyneuritis of the legs. He was given thiamine hydrochloride until he was almost free from pain. While he was still taking thiamine, after having received 21 mg. of diethylstilbestrol within seven days, mild cheilosis appeared, the nasal mucosa became painful and numbness and paresthesias developed in the hands.

CASES 4 AND 5.—We have observed 2 patients, 1 with a carcinoma and the other with alcoholic cirrhosis of the liver, in whom scaling and seborrheic lesions about the lips occurred after the administration of diethylstilbestrol. However, both these patients left the hospital before our observations were completed.

In the following cases the symptoms of vitamin B complex deficiency occurred after the administration of estrogens in the absence of a known pathologic condition of the liver.

CASE 6.—Mrs. L. H., a 52 year old white woman, was first seen in October 1940, when she complained of menopausal symptoms, headaches and severe muscle pains in the arms and legs. A complete hysterectomy had been performed in 1925.

Her physical examination revealed nothing relevant other than a blood pressure which persisted at about 170 systolic and 100 diastolic.

Because of the menopausal symptoms, she was given 60,000 international units of estrogen in the form of estrons (theelin) during thirty days, without obvious improvement. During November 1940 she was given 3 mg. of diethylstilbestrol orally each day for four days, at which time severe nausea developed. Severe glossitis appeared, with fissures and scaling at the corners of the mouth. She also complained

of a painful nasal mucosa. These lesions persisted for three months, despite treatment with daily intramuscular injections of 2 cc. of liver extract.

This patient gave no evidence of vitamin deficiency before the administration of the estrogen. After receiving 60,000 units of estrogen (estrone) in thirty days, she was given 12 mg. of diethylstilbestrol within four days. After four days of medication with diethylstilbestrol, cheilosis and painful nasal mucosa developed. Nausea occurred at the same time and could hardly be the cause of an acute vitamin deficiency.

CASE 7.—T. R., a 28 year old white woman, unmarried, had for five years all the clinical manifestations of generalized scleroderma and extremely painful peripheral neuritis. Marked muscular atrophy was accompanied by limitation of motion in all joints. She had had amenorrhea, except for atypical menses, for two years.

The peripheral pains were almost completely relieved by intramuscular injections of liver extract.

In August 1940 the patient had an almost normal menstrual period, during which time she was nearly free from subjective symptoms. From August to September 26 she was given 1 mg. of diethylstilbestrol orally each day. On September 10 severe polydypsia and polyuria developed, which have persisted to the present time (March 1941). The level of blood sugar was normal, and no glycosuria had been observed.

On September 16 she complained of severe glossitis, painful fissures at the angles of the mouth, cheilotic lesions of the lips and a painful nasal mucosa. During this time she was free from pain, but the other symptoms continued until September 26, when the diethylstilbestrol was discontinued. She was given parenteral injections of 4 cc. of liver extract daily. After one week all lesions had completely disappeared.

This young woman probably had had a vitamin deficiency during the past five years, as evidenced by the relief of the peripheral neuritis by the intramuscular injection of liver extract.

COMMENT

Study of the literature reveals that the effect of estrogen observed in these cases is not entirely unexpected. We have previously noted the tendency to exacerbation of the symptoms of pellagra during the menstrual cycle.[1b] One of the early symptoms observed in all these patients was a tender and painful nasal mucosa. Mortimer, Wright and Collip [5] observed a cyclic change in the nasal mucosa of monkeys (Macaca mulatta) at intervals of about twenty-eight days, the peaks being chiefly at "premenstrual time." This response is produced in the intact animal by administration of crystalline estrone (theelin), estriol (theelol) and emmenin. The change is seen clearly in the middle and inferior conchae

5. Mortimer, H.; Wright, R. P., and Collip, J. B.: The Effect of the Administration of Oestrogenic Hormones on the Nasal Mucosa of the Monkey (Macaca Mulatta), Canad. M. A. J. **35**:503-513 and 615-621, 1936.

as reddening and/or swelling of the mucosa. The effect is produced in immature and mature male and female animals and in female castrates.

The lesions noted in the mucous membrane of the mouth are possibly similar to those observed by Ziskin and Blackberg.[6] Castration of the female rhesus monkey causes alteration of the arrangement of the prickle cell layer of the alveolae gingivae and tissue degeneration, and hypophysectomy causes marked degenerative changes in gingival and oral mucous membranes. Castration of male rhesus monkeys causes changes in the gingival and oral mucous membranes resembling the effects of injection of estrogens namely, hyperkeratinization.

There is ample evidence that estrogens depress the activity of the anterior lobe of the pituitary or that they may cause actual anatomic changes if administered to excess. Cramer and Horning [7] observed that mice treated over a long period with estrone manifested a condition of cachexia similar to that seen in Simmonds' disease. At autopsy they found degenerative changes in the adrenal glands, hypertrophy of the islands of Langerhans and tumors (chromophobe adenomas) of the pituitary, as well as functional changes resembling those occurring after hypophysectomy.[8] Morphologically, hyperplasia of the anterior lobe occurs, in which, however, the number of chromophil cells is greatly diminished and the enlarged anterior lobe consists mainly of chromophobe cells. There is intense congestion of the anterior lobe, which may lead to hemorrhages, together with extensive production of colloid. Lacassagne [9] confirmed the report by Cramer and Horning. McEwen, Selye and Collip [10] observed adenoma of the pituitary both in male and in female rats given estrone over a long period.

In all but cases 6 and 7 a pathologic condition was known to be present in the liver. Sydenstricker [11] prepared an extract from the liver of a patient dying of uncomplicated pellagra and determined that the anti-pernicious-anemia factor was present. However, 2 patients with pellagra showed no response whatever when treated with this extract.

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6. Ziskin, D. E., and Blackberg, S. N.: Effect of Castration and Hypophysectomy on Gingival and Oral Mucous Membranes of Rhesus Monkeys, J. Dent. Research **19**:381-390, 1940.

7. Cramer, W., and Horning, E. S.: The Effect of Oestrin on the Pituitary Gland, Lancet **1**:247, 1936.

8. Cramer, W., and Horning, E. S.: Experimental Production by Oestrin of Pituitary Tumors with Hypopituitarism and Mammary Cancer, Lancet **1**:1056, 1936.

9. Lacassagne, A.: A Comparative Study of the Carcinogenic Action of Certain Oestrogenic Hormones, Am. J. Cancer **28**:735, 1936.

10. McEwen, C. S.; Selye, H., and Collip, J. B.: Some Effects of Prolonged Oestrin Administration in Rats, Lancet **1**:775, 1936.

11. Sydenstricker, V. P., in Harris, S., and Harris, S., Jr.: Clinical Pellagra, St. Louis, C. V. Mosby Company, 1940, chap. 16, p. 267.

Both responded later to a commercial liver extract. The presence of hepatic damage may interfere with the utilization and storage of the vitamin B complex or increase the requirement, as it does in the case of carotene (provitamin A), vitamin D and vitamin K. The administration of estrogens (estradiol is destroyed by the liver) may further increase the demand for vitamin B complex or may prevent its utilization directly by action on the tissue or indirectly by suppressing the activity of the anterior lobe of the pituitary.

In cases 1 and 3 (and cases 4 and 5, for which we mentioned the records were incomplete) the patients were given the full ward diet of the Cook County Hospital. Although the vitamin B complex value of this diet has not been accurately determined, it is sufficient to cause complete recovery of the polyneuritis and mild pellagra occurring in young persons addicted to alcohol.

The patients in cases 2, 6 and 7 were private patients on adequate diets generally considered to contain the ordinary requirement of vitamins. Nausea occurred only in case 6, and even in this case its duration was too short to have been an etiologic factor in vitamin deficiency.

In all cases reported, after administration of estrogenic substances, evidence of vitamin B complex deficiency appeared, namely, cheilotic lesions, or ariboflavinosis; glossitis, cutaneous lesions and psychosis, or nicotinic acid deficiency, and polyneuritis, or thiamine deficiency. Such disturbances have not been reported in articles dealing with the treatment of the menopause. This omission may not be inconsistent with our observation, since gonadotropin is excreted in the urine by women in the menopause, and the full therapeutic effect of estrogen is generally not considered to be achieved until enough has been given to cause the gonadotropin to disappear almost completely from the urine. The endocrine condition of our patients is not necessarily comparable to that of the menopausal patient. In addition, our patients had a vitamin B complex deficiency, and some had a pathologic condition of the liver.

The observations reported here and in our preceding articles strongly indicate a relation between the endocrine glands and the vitamin B complex, since the administration of an extract of the anterior lobe of the pituitary containing the growth-stimulating and gonadotropic factors cures or controls the lesions of a vitamin B complex deficiency when they are not entirely relieved by administration of the complex, and since the administration of estrogens induces or exaggerates the lesions of such a deficiency. Our observations present the problem but provide no definite explanation. We suspect that the anterior lobe of the pituitary secretes a hormone which directly or indirectly facilitates the utilization of the vitamin B complex and that estrogens either increase the demand for this hormone or suppress its secretion. The role the liver may play in the process is not so readily postulated.

CONCLUSIONS

1. The administration of estrogens to persons with a subclinical vitamin B complex deficiency may cause the appearance of lesions characteristic of a (*a*) thiamine deficiency (polyneuritis), (*b*) nicotinic acid deficiency (pellagra) or (*c*) riboflavin deficiency (cheilosis).

2. It appears obvious that the estrogens do not aid in the utilization of the vitamin B complex. According to our observation, they appear either to increase the demand for or to suppress the utilization of the vitamin B complex. The role that the damaged liver may play is uncertain.

3. The appearance of tenderness and pain in the nasal mucosa appears to be a symptom of the full physiologic effect of estrogen similar to the changes in the vaginal mucosa, particularly in persons with a vitamin B complex deficiency.

4. These observations should not be interpreted in any way as a contraindication to the use of estrogens in the treatment of ovarian deficiency, as the patients whose cases are reported here gave evidence of vitamin B deficiency before therapy with an estrogen was begun.

ORTHOSTATIC CIRCULATORY INSUFFICIENCY

ITS OCCURRENCE IN TABES DORSALIS AND ADDISON'S DISEASE

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The maintenance of an adequate circulation despite change in posture, as from the horizontal to the vertical position, is accomplished by mechanisms which insure an equitable distribution of blood. In normal persons, the assumption of an erect position is attended by an increase in peripheral vasoconstriction, particularly in the arterioles of the splanchnic area,[1] by acceleration of the heart [2] and by a greater tonus of the skeletal musculature.[3] Impairment of the capacity for postural adaptation, as a result of the failure of any of these factors, favors the development of orthostatic circulatory insufficiency, with stasis of blood in dependent areas and reduction of the cerebral blood supply. As a rule, this defect is temporary and occurs in patients weakened by illness.[4] However, it is not uncommon in persons with low blood pressure,[5] with a history of postural symptoms and a condition of noticeably subnormal

From the second medical service (Dr. Eli Moschcowitz) of the Mount Sinai Hospital.

1. (*a*) Hill, L.: The Influence of the Force of Gravity on the Circulation of Blood, J. Physiol. **18**:15, 1895. (*b*) Hill, L., and Barnard, H.: The Influence of the Force of Gravity on Circulation, ibid. **21**:323, 1897. (*c*) MacDowall, R.: The Control of the Circulation of the Blood, New York, Longmans, Green & Company, 1938, chap. 19, p. 439.

2. MacWilliam, J. A.: Postural Effects on Heart Rate and Blood Pressure, Quart. J. Exper. Physiol. **23**:1 (Aug.) 1933.

3. (*a*) Henderson, Y.; Oughterson, A. W.; Greenberg, L. A., and Searle, C. P.: Muscle Tonus, Intramuscular Pressure and the Venopressor Mechanism, Am. J. Physiol. **114**:261 (Jan.) 1936. (*b*) Mayerson, H. S., and Burch, G. E.: Relationships of Tissue (Subcutaneous and Intramuscular) and Venous Pressures to Syncope Induced in Man by Gravity, ibid. **128**:258 (Jan.) 1940.

4. Weiss, S.: Syncope and Related Syndromes, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, vol. 2, pt. 1, p. 250.

5. Lutterloh, C. H.: The Clinical Significance of the Effects of Posture on Blood Pressure: The Postural Test as a Means of Classifying Hypotension, Am. J. M. Sc. **193**:87 (Jan.) 1937.

weight [6] or with the "effort syndrome." [7] It occurs not infrequently in normal subjects at high altitudes, after strenuous exercise [8] or merely on standing immobile,[2b] for example, in a soldier standing at attention. Anesthesia, shock and various unconscious states are associated with the depression of compensatory responses, and under these conditions any change from the horizontal position endangers life.[9] Fall in blood pressure, narrowing of the pulse pressure and increasing tachycardia, as well as vertigo and syncope, after assumption of an erect posture are sensitive indications of difficulty in offsetting the effect of gravity on the blood column.[10] The principal causes of this form of circulatory insufficiency include lowering of the tonus of the vasomotor system,[11] excessive capillary dilatation,[8] hypotonus of the skeletal muscles [3] and diminished venous tone.[12]

Insufficiency of circulation during maintenance of the erect position, usually temporary and mild, may be extreme and persistent, as it was in 3 patients whose cases were reported, in 1925, by Bradbury and Eggleston [13] as examples of a new syndrome, "postural hypotension." In each case, rising from a recumbent to a standing position was attended by a prompt, pronounced fall in systolic and in diastolic blood pressure, a slow unchanging pulse rate, dizziness and syncope. Additional findings were (*a*) increased distress during the heat of summer, (*b*) anhidrosis, (*c*) signs of slight and indefinite disease of the central nervous system, (*d*) high normal blood urea, (*e*) anemia and (*f*) a low basal metabolic rate. Results of pharmacologic studies indicated that the responsiveness of the vasoconstrictor endings to epinephrine was impaired or lost. The vascular reactions were those "which would be expected if the whole peripheral vascular bed were always wide open, inelastic and capable of accommodating the major portion of the blood

6. Ghrist, D. G.: Variations in Pulse and Blood Pressure with Interrupted Change in Posture, Ann. Int. Med. **4**:945 (Feb.) 1931.

7. Lewis, T.: The Soldier's Heart and the Effort Syndrome, ed. 2, London, Shaw & Sons, Ltd., 1940.

8. Mateef, D., and Schwartz, W.: Die orthostatische Kreislaufkollaps, Gravitationsshock, bei verminderten Luftdrück, Arch. f. d. ges. Physiol. **236**:77, 1935.

9. Best, C. H., and Taylor, M. M.: Physiological Basis of Medical Practice, Philadelphia, William Wood & Company, 1937, p. 220. Hill.[1a] Hill and Barnard.[1b]

10. Schneider, E. C., and Truesdall, H.: A Statistical Study of Pulse Rate and the Arterial Blood Pressures in Recumbency, Standing and After a Standard Exercise, Am. J. Physiol. **61**:429 (Aug.) 1922. Crampton, C. W.: The Gravity Resisting Ability of the Circulation: Its Measurement and Significance, Am. J. M. Sc. **160**:721 (Nov.) 1920.

11. Hill.[1a] Hill and Barnard.[1b]

12. Weiss, S., and Haynes, F.: The Nature of Circulatory Collapse Induced by Sodium Nitrite, J. Clin. Investigation **16**:73 (Jan.) 1937.

13. Bradbury, S., and Eggleston, C.: Postural Hypotension: Report of Three Cases, Am. Heart J. **1**:73 (Oct.) 1925.

volume of the body." The syndrome was believed to be due to some extensive and peculiar disturbance in the functional capacity of the vegetative nervous system.

Analysis of 50 adequately studied cases of "postural," or "orthostatic," hypotension reported since 1925 indicated that this syndrome is not a uniform clinical entity.[14] (Twenty-four cases [15] were excluded

14. (*a*) Ghrist, D., and Brown, G. E.: Postural Hypotension with Syncope: The Successful Treatment with Ephedrine, Am. J. M. Sc. **175**:336 (March) 1928. (*b*) Ashworth, O. O.: Postural Hypotension: Report of Two Cases, Virginia M. Monthly **56**:260 (July) 1929. (*c*) Riecker, H. H., and Upjohn, E. G.: Postural Hypotension, Am. Heart J. **6**:225 (Dec.) 1930. (*d*) Strisower, R.: Ueber bedeutende Blutdrucksenkung nach Arbeit und bei Änderung der Körperlage bei Tabes dorsalis, Ztschr. f. klin. Med. **117**:384, 1931; Weitere Beiträge zur Blutdruckregulationsstörung der Tabiker, Wien. med. Wchnschr. **83**:122 (Jan. 21) 1933. (*e*) Barker, N. W., and Coleman, J. H.: Postural Hypotension Associated with Arteriosclerosis, M. Clin. North America **15**:241 (July) 1931. (*f*) Sanders, A. O.: Postural Hypotension: A Case Report, Am. J. M. Sc. **182**:217 (Aug.) 1931; Postural Hypotension with Tachycardia, Am. Heart J. **7**:808 (Aug.) 1932. (*g*) Duggan, L. B., and Barr, D. P.: Postural Hypotension Occurring in a Negro with Addison's Disease, Endocrinology **15**:531 (Nov.-Dec.) 1931. (*h*) Laubry, C., and Doumer, E.: L'hypotension orthostatique, Presse méd. **40**:17 (Jan. 6) 1932. (*i*) Lian, C., and Blondel, A.: L'hypotension artérielle orthostatique, Paris méd. **1**:179 (Feb. 25) 1933. (*j*) Barker, N. W.: Postural Hypotension: Report of a Case and Review of the Literature, M. Clin. North America **16**:1301 (May) 1933. (*k*) Allen, E. V., and Magee, H. R.: Orthostatic (Postural) Hypotension with Syncope, ibid. **18**:585 (Sept.) 1934. (*l*) Ganshorn, J. A., and Horton, B. T.: Postural Hypotension: Report of a Case, Proc. Staff Meet., Mayo Clin. **9**:541 (Sept. 12) 1934. (*m*) Weis, C. R.: Postural Hypotension with Syncope: Report of a Case Cured with Ephedrine Sulphate, Ann. Int. Med. **8**:920 (Feb.) 1935. (*n*) Croll, W. F.; Duthie, R. J., and MacWilliam, J. A.: Postural Hypotension: Report of a Case, Lancet **1**:194 (Jan. 26) 1935. (*o*) Alvarez, W. C., and Roth, G.: Postural Hypotension: Report of a Case with Some Unusual Features, Proc. Staff Meet., Mayo Clin. **10**:483 (July 31) 1935. (*p*) Hughes, T. A., and Yusaf, M.: Postural Hypotension with Tachycardia, Lancet **1**:1101 (May 11) 1935. (*q*) Chew, E. M.; Allen, E. V., and Barker, N. W.: Orthostatic Hypotension: Report of Six Cases and Review of the Literature, Proc. Staff Meet., Mayo Clin. **11**:535 (Aug. 19) 1936. (*r*) Langston, W.: Orthostatic Hypotension: Report of a Case, Ann. Int. Med. **10**:688 (Nov.) 1936. (*s*) MacLean, A. R., and Horton, B. T.: Myasthenia Gravis with Postural Hypotension, Proc. Staff Meet., Mayo Clin. **12**:787 (Dec. 15) 1937. (*t*) Ellis, L. B., and Haynes, F. G.: Postural Hypotension with Particular Reference to Its Occurrence in Disease of the Central Nervous System, Arch. Int. Med. **58**:773 (Nov.) 1936. (*u*) Korns, H. M., and Randall, W. L.: Orthostatic Hypotension Treated with Benzedrine, Am. Heart J. **13**:114 (Jan.) 1937. (*v*) Davis, P. L., and Shumway, M.: Orthostatic Hypotension: Treatment of Two Cases with Benzedrine, J. A. M. A. **108**:1247 (April 10) 1937. (*w*) Capaccio, G. D., and Donald, C. J.: Orthostatic Hypotension: Report of a Case Treated with Neosynephrin Hydrochloride, ibid. **110**:1180 (April 9) 1938. (*x*) Gillespie, D. L., and Barker, N. W.: Orthostatic Hypotension: Report of Two Cases in

(Footnotes continued on next page)

from the total number because of insufficient clinical data or because the postural defect was slight and transient.) The only constant and characteristic feature of these cases was an immediate and persistent fall in blood pressure on standing. In two thirds of the cases there was a drop in systolic pressure of at least 50 mm. of mercury, with a smaller, corresponding change in diastolic pressure, while in the remainder the fall in blood pressure was less. Orthostatic vertigo and syncope were common, but some patients with marked fluctuations in blood pressure were relatively asymptomatic, in contrast to others who were intolerant of slight changes. The erect position had a variable effect on pulse rate. In half the subjects the heart failed to accelerate normally on standing; in an equal number cardiac acceleration was normal or excessive. Hypofunction of the sweat glands, varying in intensity and extent, was mentioned in slightly more than one third of the cases. Seventy-five per cent of the patients were male, and 50 per cent were 50 years of age or older.

Of particular interest was the problem of the cause of deficient postural compensation in these cases. In most instances the condition occurred in otherwise healthy persons, and the syndrome was regarded as an abnormality of the sympathetic nervous system in which a failure of reflex vasoconstriction accompanied change to an erect position. Both the nature and the site of the pathologic process causing this abnormality were obscure. However, in about one quarter of the reported cases postural hypotension was associated with disease of the nervous system,[16]

Which Patients Were Children, J. Pediat. **12**:772 (June) 1938. (*y*) Janzen, R.: Orthostatische Kollapszustände, Klin. Wchnschr. **17**:622 (April 30) 1938. (*z*) Ewert, B.: Ueber orthostatische Krieslaufstörungen, Eine klinisch-electrokardiographische Studie, Cardiologica **2**:107, 1938. (*a'*) Baker, T. W.: Recognition of Orthostatic Hypotension, Proc. Staff Meet., Mayo Clin. **13**:169 (March 16) 1938. (*b'*) Thomas, H. M.: Transient Paralysis from Postural Hypotension, Bull. Johns Hopkins Hosp. **65**:329 (Oct.) 1939. (*c'*) Browne, H. C., and Horton, B. T.: Postural Hypotension, Hourly and Daily Pressure Variations, Minnesota Med. **22**:302 (May) 1939. (*d'*) Brewster, E. J.: Orthostatic Hypotension: Case Report Mentioning Effective Treatment with Benzedrine Sulphate, Ann. Int. Med. **14**:326 (Aug.) 1940.

15. (*a*) Schellong, F.: Störung der Kreislaufregulation, eine neues Symptom bei Insuffizienz des Hypophysenvorderlappens, Klin. Wchnschr. **10**:100 (Jan. 17) 1931; Weiteres über das Symptom der Blutdrucksenkung nach Korperarbeit, ibid. **11**:53 (Jan. 9) 1932. (*b*) Laubry and Doumer,[14h] cases 4 and 5. (*c*) Rudsit, K.: Zur Behandlung vasoneurotischer Störungen mit Hypophysenvorderlappenprepäraten mit besonderer Rücksicht auf die Blutdruckreaktion bei Aenderung der Körperlage, Wien. klin. Wchnschr. **47**:878 (July 13) 1934. (*d*) Ratner, J.: Die hypophysarsuprarenale Insuffizienz und das Schellong-Strisowersche Phänomen, Ztschr. f. klin. Med. **127**:713, 1935. (*e*) Janzen,[14y] cases 3 and 4. (*f*) Gillespie and Barker,[14z] case 2.

16. Strisower.[14d] Allen and Magee.[14k] Croll, Duthie and MacWilliam.[14n] Ellis and Haynes.[14t] Ewert.[14z] Baker.[14a'] Thomas.[14b']

myasthenia gravis [145] or adrenal insufficiency.[146] Association with such conditions suggested the relation of orthostatic circulatory disorders to nervous and endocrine dysfunction and indicated the need of investigating all cases of inadequate postural adaptation for etiologic factors.

It is the purpose of this communication to illustrate the foregoing material by the report of 3 cases of tabes dorsalis and 1 case of Addison's disease in which impressive defects in postural adaptation were observed. In addition, results of studies regarding carotid sinus hypersensitivity and the use of desoxycorticosterone acetate in treating patients with orthostatic circulatory difficulties will be presented.

REPORT OF CASES

CASE 1.—A 59 year old white salesman was admitted to the second medical service of Mount Sinai Hospital on Nov. 1, 1939 because of weakness and frequent fainting. He acquired syphilis at the age of 20 and received two courses of antisyphilitic therapy, the first when he was 20 and the second when he was 40. In 1932 he noticed the onset of recurrent epigastric pain, weakness and vertigo. He had episodes of nausea and vomiting, often terminating in syncope. Since 1937 he found it difficult to rise from a recumbent to a standing position because of weakness, vertigo and occasional syncope on the assumption of the erect posture. Getting out of bed in the morning became a trying task, requiring repeated attempts to stand. Standing for a short time or tilting the head back to look up led to uncomfortable weakness and dizziness. Lowering the head between the legs or assuming a recumbent position promptly relieved these symptoms. He became completely incapacitated and was unable to engage in any form of sustained effort. On the day of admission to the hospital he fainted while being examined by a physician, who advised hospitalization.

Physical Examination.—The patient appeared emaciated and chronically ill. His teeth were dirty and carious. There was a small angioma on the right buccal mucous membrane, but no buccal pigmentation. The right optic disk was pale; the left, normal. The choroidal vessels could be easily seen and formed a yellow gyrate pattern, indicating well marked choroidal sclerosis. The pupils were round, in mid-dilatation and fixed to light and in accommodation. The lungs were clear. The heart sounds were poor, but the heart was otherwise normal. The abdomen was scaphoid, with lax walls. Generalized muscular hypotonia, especially in the lower extremities, was detected on neurologic examination; deep reflexes were diminished in the upper extremities and were not elicitable in the lower, even with reenforcement. The abdominal reflexes were present but exhaustible. There were no pathologic reflexes. Touch sensation (cotton wool) was relatively normal. Sensitivity to pinprick was diminished in both lower extremities to the inguinal regions and in both arms to above the elbows. There were narrow, poorly defined bands of hypalgesia on the trunk; vibratory sensation was absent in both lower extremities to above the iliac crests. Position sense was lost in the toes and in the fingers of the left hand. Deep tendon pain was diminished.

When the patient stood erect, he swayed noticeably, became weak, and had to be supported to prevent his falling. A pulse could not be palpated at the wrist while he was in the erect position. His blood pressure while he was standing was 60 systolic and 50 diastolic as compared with 120 systolic and 80 diastolic

measured a few minutes before while he had been recumbent. The clinical impression was tabes dorsalis associated with postural hypotension, which was apparently the basis for the recurrent dizziness and fainting.

Laboratory Data.—The concentration of hemoglobin was 86 per cent (100 per cent = 16 Gm. per hundred cubic centimeters), and the white blood cell count was 7,700, with 71 per cent polymorphonuclear leukocytes, 2 per cent eosinophils, 5 per cent monocytes and 22 per cent lymphocytes. The urine was clear with an acid reaction, a specific gravity of 1.020, a faint trace of albumin and, on microscopic examination, an occasional white blood cell. Gastric analysis showed normal acidity. Chemical analysis of the blood revealed urea nitrogen to be 16 mg. per hundred cubic centimeters; sugar, 95 mg. per hundred cubic centimeters; total protein, 7.2 Gm. per hundred cubic centimeters, and icteric index, 3. The result of the dextrose tolerance test was normal. After three days of a salt-poor diet containing less than 1 Gm. of sodium chloride daily, the content of sodium in the blood was 140 milliequivalents per liter. The Wassermann reaction of the blood was negative. Lumbar puncture yielded crystal clear spinal fluid under normal pressure. The fluid contained 55 lymphocytes per cubic millimeter. The reaction for globulin was positive. The Wassermann reaction of the spinal fluid was 4 plus, and the colloidal gold curve was paretic in type. The total protein content of the spinal fluid was 72 mg. per hundred cubic centimeters.

The basal metabolic rate was —30 per cent. The venous pressure was 4.5 cm. of blood, with no rise on pressure on the right upper quadrant of the abdomen for one minute. An electrocardiogram showed regular sinus rhythm, left axis deviation and semi-inversion of the P and T waves in lead III.

Effect of Posture on Blood Pressure and Pulse Rate—Elevation of the patient on a mechanical tilt table 80 degrees above the horizontal was attended by an immediate fall in the systolic and the diastolic blood pressure from 120 to 60 and from 70 to an undetermined figure, respectively; the pulse rate increased from 72 to 86. Sudden lowering of the patient to the horizontal was accompanied by a return of blood pressure to normal. The fall in blood pressure on elevation could not be prevented by the application of an abdominal binder.

Effect of Vasoconstrictor Substances.—Intravenous injection of 2 minims (0.12 cc.) of a 1 : 1,000 solution of epinephrine hydrochloride caused a rise in blood pressure to 240 systolic and 140 diastolic ten seconds after injection and an acceleration of the pulse rate to 190. The fall in blood pressure during maintenance of the erect posture was prevented for nine minutes. Inhalation of a mixture of 25 per cent carbon dioxide and 75 per cent oxygen caused a rise in blood pressure from 120 to 240 systolic and from 80 to 120 diastolic after thirty seconds of administration of the gas with the patient in a horizontal position. Elevation of the patient was attended by a fall in blood pressure to hypotensive levels within two minutes. The mixture of gases produced no pressor response if the patient maintained an erect position after the blood pressure had fallen; however, resumption of a horizontal position after this stimulus had been removed was followed by a transient pressor response. Intravenous administration of 10 mg. of paredrinol (α-N-dimethyl-p-hydroxyphenethylamine) caused a rise in blood pressure to 240 systolic and 120 diastolic and prevented the fall in blood pressure for ten minutes. These findings indicated the sensitivity of the vasoconstrictor endings to pressor influences.

Stimulation of the Carotid Sinus.—Mechanical stimulation of the right carotid sinus with the patient recumbent was associated with bradycardia, a fall in the

systolic and the diastolic blood pressure, syncope and generalized convulsions. Periods of asystole, lasting seven to eight seconds, were recorded electrocardiographically during sinus stimulation. These phenomena could be elicited more easily and more frequently with the patient in the sitting position. The left carotid sinus was less sensitive to stimulation than the right. Apparently, none of the symptoms were related to sudden turning of the head or wearing of a tight collar, factors often precipitating syncope in cases of the carotid sinus syndrome.

Circulation Time.—The circulation time was measured as the patient was placed in various positions with the aid of a mechanical tilt table. Three cubic centimeters of a 20 per cent solution of decholin sodium and 2.5 Gm. of saccharin in 3 cc. of distilled water were used as test substances and were injected into a right antecubital vein. The decholin end point, a bitter taste, was sharper than the saccharin point, a sweet taste. At the time of the first determination the patient's blood pressure fell from 88 systolic and 64 diastolic in the horizontal position to 40 systolic and an undetermined diastolic level in the vertical position. When he was in the former position the circulation time of decholin was twenty-two seconds and that of saccharin twenty-six seconds. When the patient was in the vertical position no satisfactory response could be obtained with either substance. When he was lowered after each failure, no definite end point was obtained. During these studies he complained of vertigo and blurring of vision in the erect posture, and it was felt that the failure to obtain a response while he was in the erect position was due in part to his inability to cooperate subjectively, a result of cerebral anemia.

Ten days later, after three days of therapy with desoxycorticosterone acetate, these studies were repeated. At this time postural hypotension was not present and the blood pressure was maintained at 110 systolic and 60 diastolic whether the patient was recumbent or erect. When he was recumbent the circulation time of decholin was nineteen seconds and the circulation time of saccharin was thirty seconds; after he assumed an erect position the respective times were sixteen and twenty-nine seconds. He was free of postural symptoms.

Treatment.—The use of a variety of drugs and mechanical measures to control the postural hypotension was without impressive benefit. Ephedrine sulfate, neosynephrin hydrochloride and paredrine hydrobromide (para-hydroxy-α-methylphenethylamine hydrochloride) in adequate doses by mouth caused little, if any, subjective and no objective improvement. A tight abdominal binder did not reenforce the postural mechanisms. Elastic bandages, from the ankles to the midthighs, were uncomfortable and did not prevent the orthostatic fall in blood pressure. On the other hand, the tabes dorsalis was controlled satisfactorily by intramuscular injection of a suspension of bismuth subsalicylate in oil for a period of eight months.

The failure to remedy the postural defect by the usual measures led to an empiric study of the effect of sodium chloride and desoxycorticosterone acetate. Preliminary administration of 9 Gm. of sodium chloride daily for ten days resulted in no definite change. However, the addition of intramuscular injections of desoxycorticosterone acetate in oil (5 mg. daily) was followed promptly by an increase in weight of from 139 to 144 pounds (63 to 65.3 Kg.) in six days and amelioration of the postural hypotension. The blood pressure could be maintained without change for five to ten minutes, while the patient remained erect, and the subsequent fall was less marked. On several occasions blood pressure readings of 150 systolic and 100 diastolic were obtained with the patient recumbent. The circulation times with the patient in the horizontal and in the vertical position

were approximately the same, in contrast to his inability before the use of desoxycorticosterone to remain erect long enough for us to obtain an end point. The patient stated that he felt more vigorous and was capable of greater physical activity. The sodium content of the blood after injections of desoxycorticosterone acetate was 145 milliequivalents per liter and the chloride content 105 milliequivalents per liter. The blood volume was 93 cc. per kilogram (congo red test). The carotid sinus hypersensitivity was unchanged.

Cessation of therapy with desoxycorticosterone acetate caused prompt reappearance of marked postural hypotension and associated symptoms. Subsequent injections of the drug were accompanied again by the same improvement, as a result suggesting a specific response. Satisfactory improvement was obtained with as little as 1.2 mg. of desoxycorticosterone acetate daily, given with 9 Gm. of sodium chloride. The use of the drug was attended by a slight transient edema of the legs and face but not by other untoward symptoms or by electrocardiographic changes.

Four pellets of crystalline desoxycorticosterone acetate, each weighing approximately 125 mg., were implanted subcutaneously below the angle of the right scapula. After implantation the patient could stand comfortably for thirty to sixty minutes. During such periods the blood pressure fell slowly from 120 to 70 systolic and from 80 to 60 diastolic. The fall was neither as marked nor as prompt as before desoxycorticosterone acetate therapy. The pellets stayed in situ for nineteen weeks, with only slight and unimpressive control of the postural hypotension after the patient left the hospital. It was felt that the daily dose supplied by these pellets (about 1.2 mg.) was inadequate for the demands of life outside the hospital. During this period extradietary sodium chloride was withheld. Supplementary injections of desoxycorticosterone acetate in oil (5 mg. two to three times weekly) seemed of some benefit, but this was less striking as compared with observations during hospitalization. When the pellets were removed, nineteen weeks after implantation, their original weight was reduced by about half. A salt deprivation test, performed two weeks later, revealed no evidence of adrenal insufficiency. After three days of deprivation the sodium content of the blood was 138 milliequivalents per liter and the chloride content 103 milliequivalents per liter. The basal metabolic rate was —14 per cent. The sugar tolerance curve was normal. However, the patient complained of increased weakness, was bedridden and had a return of pronounced orthostatic hypotension. Restitution of daily injections of 5 mg. of desoxycorticosterone acetate in oil led to a gain in weight, a rise in blood pressure and a more sustained blood pressure during maintenance of an erect position.

Case 2.—A 54 year old white man, a German refugee, was admitted to the second medical service on July 11, 1940 because of weakness, vertigo and vomiting for one month. On a previous admission to the hospital, in May 1940, a diagnosis of tabes dorsalis and cord bladder was made. At that time moderate loss in weight, thin lax abdomen, palpable liver, absence of ankle and knee jerks, positive Biernacki and Abadie signs and loss of vibratory sensation over the sacral area were observed. The pupils were irregular but reacted well to light and in accommodation. Repeated Wassermann tests of the blood gave negative results, even after provocative injections of a suspension of bismuth subsalicylate in oil and neoarsphenamine. The Wassermann reaction of the spinal fluid was positive. The colloidal gold curve was tabetic in type.

Shortly after discharge the patient began to vomit frequently, especially in the morning after getting out of bed. He felt weak and dizzy at such times and noticed that his symptoms, especially vertigo, were relieved by lying down.

The patient was seen by one of us (W. M. H.) in the outpatient clinic, and his history associated with the tabes prompted a study of the effect of posture on pulse and blood pressure. A definite postural fall in blood pressure was noted, and the patient was readmitted to the hospital for study. Results of the physical examination were unchanged from the time of his first admission. There was no evidence of abnormal sweating; the urine contained albumin and many white blood cells; the electrocardiogram was normal; the basal metabolic rate was —15 per cent; the blood count was normal; the blood per hundred cubic centimeters contained 17 mg. of nitrogen and 610 mg. of chlorides; its carbon dioxide-combining power was 59.5 volumes per cent, and the Wassermann reaction of the blood was negative.

Postural Studies.—Rising from a horizontal to a vertical position led to an immediate fall in blood pressure from 110 to 75 systolic and from 70 to 50 diastolic. Standing for five minutes led to a further drop, to 60 systolic and 50 diastolic. The pulse rate increased from 78 when the patient was in the horizontal position to 88 when he was in the vertical position. Similar results were obtained during passive elevation of the patient on a mechanical tilt table. The degree of the orthostatic fall varied from day to day but was always present and was most marked in the morning. The circulation time of decholin was fifteen seconds both when the patient was recumbent and when he was standing. Pressure on the right carotid sinus with the patient upright led to an imperceptible pulse, mild collapse and transient blurring of vision. Sinus stimulation with the patient recumbent produced neither symptoms nor changes in pulse and blood pressure.

Treatment.—Daily injections of 5 mg. of desoxycorticosterone acetate in oil were given for sixteen days. This therapy was associated with a rise in blood pressure. Readings of 150 systolic and 90 diastolic were obtained often while the patient was recumbent, as compared with the reading of 110 systolic and 70 diastolic made on admission. Although an orthostatic fall in blood pressure persisted, a higher pressure could be maintained for a considerably longer period while he was erect. When he maintained a vertical position for thirty minutes, his blood pressure dropped from 120 to 90 systolic and 78 to 64 diastolic. The patient gained weight and said he felt much improved.

Case 3.—A white woman aged 44 was admitted to the service of Dr. I. S. Wechsler on Aug. 11, 1940. Her chief complaint was pain in the back and legs for four years. In 1936 a routine Wassermann reaction of the blood was positive. She had received antisyphilitic therapy for eighteen months and then discontinued treatment, despite the fact that her serologic reactions were still positive. Throughout treatment and up to the time of admission she experienced episodes of numbness and tightness across the chest and recurrent shooting pains arising in the lumbar region and radiating down both legs. About one year before entry she noticed the onset of vertigo, weakness and frequent headaches. These symptoms were relieved by lying down and were precipitated by rising from the recumbent position, particularly on attempting to get out of bed in the morning.

Physical Examination.—The patient was well developed and somewhat euphoric, with small irregular pupils which reacted adequately to light and in accommodation. The heart was enlarged. The aortic second sound was loud and bell-like. The lungs were clear. Deep reflexes were hyperactive in both upper extremities. The left knee jerk and the ankle jerks could not be obtained. Superficial reflexes were intact. There was a positive Abadie sign on the left. Deep sensation was diminished and delayed on the right. Vibratory position and superficial sense modalities were normal. The clinical impression was tabes dorsalis.

Laboratory Data.—The urine and the blood count were normal. The spinal fluid was clear and under normal pressure; it contained 7 monocytes per cubic millimeter and had a total protein content of 60 mg. per hundred cubic centimeters. The colloidal gold curve was tabetic in type. The Wassermann reactions of the blood and the spinal fluid were positive. The blood per hundred cubic centimeters contained 15 mg. of urea nitrogen and 80 mg. of sugar.

Postural Reactions and Carotid Sinus Reflexes.—The history of postural symptoms prompted the study of the effect of changes in posture on pulse rate and blood pressure. A definite orthostatic fall in blood pressure associated with increasing tachycardia was observed. The blood pressure dropped from 152 to 108 systolic and remained at 88 diastolic within seven minutes after a change from a recumbent to an erect posture. This was associated with an increase in pulse rate from 90 to 124 beats per minute and the onset of weakness, vertigo and profuse diaphoresis.

Pressure on the right carotid sinus with the patient recumbent produced immediate asystole followed within a few seconds by syncope and clonic convulsions. Similar results followed pressure on the left carotid sinus. Atropinization abolished the abnormal sensitivity of the carotid sinus to mechanical stimulation. There was no history of spontaneous symptoms attributable to this sensitivity.

Course and Treatment.—The patient was treated with tryparsamide, without any disturbance in visual fields or acuity. Because of her orthostatic defect, she was given 25 mg. of ephedrine sulfate three times daily. The use of the drug, during a three week period of observation, was associated with dramatic relief of vertigo and weakness while standing. There was no change in the vascular reactions or in the degree of carotid sinus sensitivity to mechanical stimulation.

Case 4.—A white man, a 46 year old delicatessen clerk, consulted one of us (W. M. H.) in August 1940. For a month he had been troubled with constant weakness and frequent episodes of vertigo. His past history included recurrent attacks of epigastric pain since 1937 and treatments for a suspected pyloric ulcer in 1939. In May 1940 while on a restricted diet for a gastric disorder, he lost weight and strength and was observed for one week in a hospital. On discharge he was unimproved. Examination had revealed no cause for his complaints. During the subsequent weeks asthenia and loss of weight continued. In addition, he found it difficult to stand because of vertigo. This symptom was associated with the erect posture and was relieved by lying down. On one occasion he fainted after a vomiting spell.

Physical Examination.—The patient appeared chronically ill, with a pressure which fell from 110 to 70 systolic and 70 to 60 diastolic after he stood for two minutes. His pulse rate increased from 80 beats per minute while he was recumbent to 108 when he stood erect. Pressure on the right carotid sinus was poorly tolerated only when he was in an erect position. There were patches of black pigmentation on the gums and buccal mucosa. The genitals were highly pigmented. The patient thought his skin was somewhat darker than previously, although the presence of a recent sun tan made it difficult to be certain. The symptoms and findings suggested Addison's disease, and on Aug. 14, 1940 he was referred to the second medical service at Mount Sinai Hospital.

On admission, the additional history of a recent craving for salty food was obtained. Physical examination confirmed the aforementioned observations. His blood pressure was 86 systolic and 60 diastolic when he was recumbent and 70 systolic and 60 diastolic after he had stood one minute. The concentration of hemoglobin was 100 per cent, and the white blood count was 7,600, with a normal dif-

ferential count. The urine was normal. The Wassermann reaction of the blood was negative. An electrocardiogram showed no abnormality. The blood per hundred cubic centimeters contained 24 mg. of urea nitrogen, 85 mg. of sugar and 525 mg. of chlorides (as sodium chloride). The sodium content of the blood was 133 milliequivalents per liter. A roentgenogram of the abdomen was negative for calcification of the adrenals. The dextrose tolerance curve was flattened. The Mantoux test was positive in a dilution of 1:100,000.

Course and Treatment.—The history, physical findings and laboratory data justified a diagnosis of Addison's disease, and therapy with sodium chloride and desoxycorticosterone acetate was started. The use of 12 Gm. of sodium chloride daily was associated with relief of weakness and a rise in weight from 133 to 140 pounds (60.3 to 63.5 Kg.) in a week. The hematocrit reading fell from 41 to 36 per cent and the blood urea nitrogen from 24 to 15 mg. per hundred cubic centimeters. The postural fall in blood pressure remained. His blood pressure while he lay recumbent was 115 systolic and 90 diastolic but dropped to 96 systolic and 66 diastolic when he stood erect. After three weeks improvement seemed stationary. Administration of extra sodium chloride was stopped, and the patient was given daily intramuscular injections of 5 mg. of desoxycorticosterone acetate in oil. After seven injections his weight increased to 148 pounds (67.1 Kg.) and his blood pressure rose to 145 systolic and 90 diastolic. Postural hypotension was no longer present. At this time the hematocrit reading was 32 per cent. The patient was scarcely recognizable; his complexion was lighter, and he stated that he felt better than he had in years.

Desoxycorticosterone acetate and extra sodium chloride were discontinued. In nine days the patient lost 10 pounds (4.5 Kg.), and the hematocrit reading rose from 32 to 40 per cent. The blood pressure dropped from 140 to 120 systolic and from 90 to 80 diastolic. However, orthostatic hypotension was not observed. To obtain metabolic evidence of adrenal insufficiency, we placed him on a salt-poor diet (containing less than 1 Gm. of sodium chloride daily) for three days. On the second day he complained of extreme weakness and fatigue, and a fall in blood pressure while he maintained an erect position was present for the first time since the use of desoxycorticosterone acetate. His blood pressure dropped from 140 systolic and 90 diastolic while he was recumbent to 110 systolic and 80 diastolic after he stood for two minutes. On the third day he complained of nausea and extreme weakness and vomited several times. He was prostrate; his blood pressure was 85 systolic and 60 diastolic, and his pulse rate was 125 beats per minute. Two hours before this episode the horizontal blood pressure was 120 systolic and 80 diastolic. He presented the picture of acute adrenal insufficiency. Intravenous administration of physiologic solution of sodium chloride and injections of desoxycorticosterone acetate were followed by prompt improvement. The content of sodium in the blood at the time of the crisis was 127 milliequivalents per liter, a level indicating adrenal cortical insufficiency.

COMMENT

The preceding cases represent varying degrees of orthostatic insufficiency of the circulation, a state characterized by falling blood pressure, diminished venous return and impaired cerebral blood supply during maintenance of an erect posture. Attacks of syncope were seen only in 1 of the patients (case 1), in whom the orthostatic fall in blood pres-

sure was immediate and most marked. The absence of syncope in many cases of postural hypotension was attributed by Barker [14j] to a compensatory increase in heart rate sufficient to maintain an adequate cardiac output. In cases in which syncope was lacking he noted that a greater increase in pulse rate was associated with falling blood pressure than in cases in which syncopal attacks were frequent and in which cardiac acceleration was usually slight or absent. In each of our cases, an increase in heart rate occurred when the patient stood erect, and in 1 (case 3) standing was accompanied by increasing tachycardia. In all cases weakness and vertigo during maintenance of an erect posture were annoying symptoms. It is interesting that the cause of these two symptoms remained obscure for a considerable period in the 3 cases of tabes dorsalis in which orthostatic difficulty was finally recognized. In our fourth case these symptoms were promptly ascribed to an inadequate postural response. This and other findings were consistent with a diagnosis of Addison's disease.

The presence of defective postural adaptation and the consequent orthostatic circulatory insufficiency in our 3 cases of tabes dorsalis illustrates the relation of nervous disease to this abnormality. Although Bradbury and Eggleston [13] noted irregular pupils and abnormal reflexes in their original report of cases of postural hypotension, Strisower [14d] was the first to report comparable orthostatic difficulty in patients with an extensive nervous disease, such as tabes dorsalis. He noted defective responses to changes in posture in 13 of 20 tabetic patients whom he studied and ascribed them to involvement of spinal vasomotor centers and tracts. Subsequently, Ellis and Haynes [14t] recorded 2 cases of tabes dorsalis with postural hypotension and noted mild postural depression of blood pressure in 8 of 15 cases of tabes. In 2 other cases of postural hypotension described in their report syringomyelia and transverse myelitis, respectively, were present. On the other hand, the study by the same authors of a group of cases of combined system disease, advanced multiple sclerosis, marked syringomyelia, amyotrophic lateral sclerosis and transverse myelitis failed to reveal an inadequate response of the blood pressure during maintenance of erect posture. These cases indicated that extensive disease of the brain and spinal cord can exist without a disturbance of the postural blood pressure reflex. Ellis and Haynes expressed the belief that the orthostatic fall in blood pressure in patients with neurologic disease resulted from damage to the vasomotor reflex arc and stated that the etiologic factor was apt to be multiple, since the reflex arc could be interrupted at different levels. They suggested that the lesion was hypothalamic rather than spinal.

Signs of a disseminated disease of the central nervous system of unknown cause were present in cases of postural hypotension reported by Ganshorn and Horton,[14l] Baker [14s'] and Ewert.[14s] Baker suggested

that patchy sclerosis of the brain and the spinal cord might be the result of the intermittently disturbed circulation of these organs incident to postural changes, rather than the cause of this form of circulatory weakness. Hemianopia and aphasia in the case of postural hypotension reported by Allen and Magee [14k] were attributed to sclerosis of the cerebral vessels. Adie's syndrome (pseudo Argyll Robertson pupil and absence of knee jerks) was noted in the case reported by Croll, Duthie and MacWilliams.[14n] Thomas [14b'] described a remarkable case of an arteriosclerotic man with postural hypotension who suffered from transient episodes of right hemiplegia in the erect posture. It is interesting that postural hypotension and regional anhidrosis have been produced by anterior rhizotomy, splanchnic resection and excision of abdominal sympathetic ganglions for severe essential hypertension.[17]

Several points are called to mind by the foregoing consideration of the occurrence of impaired orthostatic circulatory adjustment in patients with nervous disease. Obviously, the recognition of such deficiency may clarify the significance of dizziness and fainting in some patients with neurologic disorders. Recognition of this abnormality, even to a mild degree, is of particular importance in any such patient before a surgical procedure or any form of therapy that may favor the onset of circulatory collapse—for example, hyperthermia or malaria therapy. Finally, it has been stated that "when the anatomic pathways of this [vasomotor] reflex have been traced with greater exactitude, the measurement of blood pressure in different bodily positions may furnish evidence as to the presence or location of a lesion of the central nervous system." [14t]

An exceptional feature of 2 of our cases (1 and 3) was the presence of hypersensitivity of the carotid sinus. In each instance, mechanical stimulation of the sinus with the patient recumbent produced cardiac asystole, a fall in blood pressure, syncope and convulsions. An analysis of 53 cases of postural hypotension and of 24 cases of a milder degree of inadequate postural adaptation revealed hypersensitivity of the carotid sinus in only 4 cases. In most reports the reactivity of the carotid sinus reflexes was not mentioned. Ellis and Haynes,[14t] who studied these reflexes in 6 cases, found a mildly hyperactive reaction in only 1, a case of tabes. Hughes and Yusaf [14p] elicited a prompt fall in pulse rate on carotid pressure in 1 case. In a case reported by Ewert [14s] stimulation of the carotid sinus was followed by asystole for several seconds and an atrioventricular block. Atropinization prevented this response. Thomas [14b'] reported a case in which pressure on the carotid sinus dur-

17. Brown, G. E.; Craig, W. McK., and Adson, A. W.: The Treatment of Severe Essential Hypertension: Effects of Surgical Procedures Applied to the Sympathetic Nervous System, Minnesota Med. **18**:134 (March) 1935.

ing maintenance of the erect posture resulted in rapid deep breathing, bradycardia and syncope. An electrocardiogram showed a dropped beat, with a ventricular pause lasting two and one-half seconds. On the other hand, in cases recorded by Browne and Horton,[14c] Davis and Shumway [14r] and Korns and Randall,[14u] no abnormalities were detected after stimulation of the carotid sinuses.

The occurrence of carotid sinus hypersensitivity in patients with orthostatic circulatory difficulties is of considerable interest, since it has been suggested that the latter abnormality may result from a disturbance of the regulating function of the carotid sinus. Normally, a fall in blood pressure within the sinus produces reflex vasoconstriction and cardiac acceleration.[18] Hering [19] reported prevention of these reflex responses in dogs by denervation of the sinuses, which process indicated a possible relation between the insensibility of the carotid pressoreceptive mechanism and the depression of blood pressure after assumption of the erect posture. Thus far, results of clinical studies have failed to support the concept of abnormal sensitivity of the carotid sinus in cases of orthostatic depression of blood pressure. Ferris, Capps and Weiss [20] found no relation between postural hypotension and hypersensitivity of the sinuses in a large carefully studied group of patients with carotid sinus syncope. In most patients with this disorder, the hypersensitive reflexes could be elicited more easily in the sitting or standing position, a fact indicating the reenforcing effect of gravity on the excessive response to stimulation. As a rule, these patients did not react adversely to posture alone. Mild postural hypotension was present in only 1 of 32 cases. Denervation of the sinus by section of the carotid sinus nerve prevented further syncopal attacks but did not lead to impairment of orthostatic adjustment. Similarly, Ask-Upmark [21] concluded that the clinical evidence does not support the contention that abnormalities of the carotid sinus reflexes are of etiologic significance in human postural hypotension.

In 2 of our cases and in the 4 cases recorded in the literature, sinus stimulation was associated with reflex bradycardia, a condition which would seem to indicate an increased vagal influence on the heart rate.

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18. Heymans, C.; Bouckaert, J. J., and Regniers, P.: Le sinus carotidien et la zone homologue cardio-aortique, Paris, Gaston Doin & Cie, 1933, p. 285.

19. Hering, H. E.: Ueber die Blutdruckregulierung bei Aenderung der Körperstellung vermittels der Blutdruckzügler und das Zustandekommen der Ohmacht beim plötzlichen Uebergang vom Liegen zum Stehen, München. med. Wchnschr. **74**:1611 (Sept. 23) 1927.

20. Ferris, E. B., Jr.; Capps, R., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Unconscious State and Convulsions, Medicine **14**:377 (Dec.) 1935.

21. Ask-Upmark, E.: The Carotid Sinus and the Cerebral Circulation, Acta psychiat. et neurol., 1935, supp. 6, p. 1.

Although the significance of the association of reflex abnormalities of cardiovascular regulation with sinus stimulation must remain a matter for speculation, it may be pointed out that carotid sinus hypersensitivity, like defective postural adaptation, may accompany nervous disease. Weiss [4] stated that "syphilis of the central nervous system seems to bear a causative relation to carotid sinus syncope." In 4 of 32 cases studied by Ferris, Capps and Weiss [20] tabes dorsalis was present. It is perhaps more than coincidental that in cases of orthostatic circulatory insufficiency with hypersensitive carotid sinus reflexes reported by Ellis and Haynes, by Ewert and by ourselves there was definite evidence of nervous disease. Consequently, lesions affecting central vasomotor reflex pathways may be the common basis for the coexistence of the two disturbances in these cases.

Two of our patients (cases 2 and 4) in whom stimulation of the carotid sinus was well tolerated when in the recumbent position reacted adversely to this procedure when standing. There was a fall in blood pressure, blurring of vision and incipient collapse after such stimulation. These responses were likely due to an increased susceptibility to slight changes in pulse and blood pressure so induced in patients with already impaired postural adaptation.

Our fourth case has been presented to indicate that orthostatic circulatory insufficiency may be a feature of Addison's disease. In this case, the clinical picture was obscure until failure to maintain a normal blood pressure in the erect posture was detected. This symptom, as well as others, led to additional studies which confirmed the presence of adrenal insufficiency. It is remarkable, and perhaps not generally known, that Addison mentioned orthostatic weakness and syncope in his first report.[22] Duggan and Barr,[14g] however, were apparently the first to record extreme postural hypotension as the cause of syncope in a case of Addison's disease. This case is unique, for we were unable to find a record of a comparable degree of postural circulatory inadequacy in a patient with this disease. However, lesser degrees of defective postural adaptation in patients with adrenal insufficiency have been observed by Ghrist,[6] Porges,[23] Hanssen,[24] Ratner [15d] and Thaddea.[25] Ghrist stated that decrease or abnormality of the circulating adrenal hormone is probably a major factor in these abnormal reactions to pos-

22. Addison, cited by Duggan and Barr.[14g]

23. Porges, O.: Ueber die Behandlung des Morbus Addison mit Cortigen und die Zusammenhänge der Krankeit mit dem Kohlenhydratstoffwechsel, Wien. klin. Wchnschr. **46**:185 (Feb. 10) 1933.

24. Hanssen, P.: Six Cases of Addison's Disease: Contributions to Diagnosis and Treatment, Acta med. Scandinav. **89**:426, 1936.

25. Thaddea, S.: Nebennierenrinde und Blutdrückregulation, Endokrinologie **21**:388, 1939.

tural change. Thaddea attributed this finding to a hypodynamic state of the vasconstrictor mechanisms as a result of cortical insufficiency. In several cases the postural fall in blood pressure was eliminated by treatment with adrenal cortical extract.[26] In our patient the inability to offset the effects of gravity on the circulation during maintenance of a standing position was not abolished until desoxycorticosterone acetate was given, despite the administration of ample sodium chloride preceding the use of this drug.

In this connection may be mentioned Schellong's [15a] report of orthostatic hypotension in patients with Simmonds' disease (anterior pituitary insufficiency). He expressed the belief that postural difficulties were an early and characteristic symptom of the disorder and noted improvement in vascular reactions with extracts of the anterior lobe. Ratner [15d] described cases of a similar condition and suggested that loss of the adrenotropic factor was primarily responsible for postural inadequacy in Simmonds' disease. Rudsit [15c] treated 5 patients who had mild orthostatic hypotension with extract of the anterior lobe and noted the disappearance of the abnormal vascular reactions. The mild nature of the postural disorder in this group of cases, as well as the difficulties inherent in the proof of the diagnosis of anterior lobe insufficiency, casts some doubt on the actual significance of some of these reports, although in 1 of Schellong's cases autopsy revealed destruction of the anterior lobe by a brain tumor.[15a]

The impaired ability of patients with Addison's disease and perhaps of those with Simmonds' disease to compensate for postural change may be the result of specific hormonal deficiency or of general physical debility. Ellis and Haynes [14t] expressed the opinion that the postural hypotension of such patients was part of a general hypofunction of the sympathetic nervous system and of the muscular hypotonicity seen in these states. In favor of a nonspecific response is the fact that postural difficulties may be seen in weakened persons, especially in those who have lost weight.[6] Recent emphasis on the importance of normal nutrition to glandular function suggests that defective postural adaptation in asthenic patients may represent temporary depression of some endocrine function. In this regard, it is interesting that Mulinos and Pomerantz [27] produced changes in the endocrine glands of rats by inanition which were similar to changes seen after hypophysectomy.

The use of desoxycorticosterone acetate in 3 cases deserves brief comment. In our patient with Addison's disease the drug produced a prompt elevation in blood pressure and led to the disappearance of the

26. Hanssen.[24] Thaddea.[25]

27. Mulinos, M. G., and Pomerantz, L.: Pseudo-Hypophysectomy: A Condition Resembling Hypophysectomy Produced by Malnutrition, J. Nutrition **19**:495 (May) 1940.

postural hypotension, which had been only partially removed by therapy with sodium chloride. Cessation of this therapy was followed by the reappearance of orthostatic circulatory weakness, which preceded the onset of an addisonian crisis. This response may be a sensitive sign of inadequate therapy in cases of adrenal insufficiency.

In 2 cases of defective postural adaptation without associated Addison's disease, several reasons prompted the trial of desoxycorticosterone. The occurrence of orthostatic difficulties in patients with Addison's disease has been mentioned. Moreover, we have observed, and recent studies have shown, that desoxycorticosterone acetate has a pronounced effect on blood pressure in patients with Addison's disease, producing prompt elevation of blood pressure to normal and in some instances appreciable hypertension.[28] It is interesting that Bradbury and Eggleston [13] considered hypoadrenia a possible cause of postural hypotension and that unsuccessful attempts to treat this defect as a manifestation of adrenal cortical hypofunction have been reported by Langston,[14r] who used adrenal cortical extract (eschatin) and by Capaccio and Donald [14w] and Davis and Shumway,[14v] who gave large doses of sodium chloride.

In the aforementioned 2 cases treatment with desoxycorticosterone acetate was associated with symptomatic improvement and with an increased capacity for physical effort. Orthostatic hypotension, though still present, developed less rapidly and frequently to a lesser extent. Both patients were able to maintain higher levels of pressure for prolonged periods in the upright position. In addition, a moderate but inconstant rise in the blood pressure occurred in the horizontal position. However, the favorable influence of the drug on vascular adaptation after assumption of an erect posture did not seem to depend on a general increase in arterial tension. Amelioration of orthostatic circulatory insufficiency was observed on several occasions in the absence of any significant elevation of the horizontal blood pressure. This change suggested that the drug led to a greater ability to maintain an adequate circulation in the upright position by some mechanism as yet undetermined. The need for utmost care in the clinical use of desoxycorticosterone has been emphasized by the serious complications that may

28. Ferrebee, J. W.; Ragan, C.; Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone Esters: Certain Effects in the Treatment of Addison's Disease, J. A. M. A. **113**:1725 (Nov. 4) 1939. McCullagh, E. P., and Ryan, E. J.: The Use of Desoxycorticosterone Acetate in Addison's Disease, ibid. **114**:2530 (June 29) 1940. Thorn, G. W., and Firor, W. M.: Desoxycorticosterone Acetate Therapy in Addison's Disease: Clinical Considerations, ibid. **114**:2517 (June 29) 1940. Soffer, L. J.; Engel, F. L., and Oppenheimer, B. S.: Treatment of Addison's Disease with Desoxycorticosterone Acetate, ibid. **115**:1860 (Nov. 30) 1940.

occur during the treatment of Addison's disease with this substance [29] and by the results of its administration in large doses to normal animals.[30]

SUMMARY

Orthostatic circulatory insufficiency, marked by falling blood pressure and by vertigo on assumption of an erect position, was observed in 3 patients with tabes dorsalis and in 1 with Addison's disease. The relation of this abnormality to nervous and to endocrine disease is reviewed briefly. Carotid sinus hypersensitivity was an unusual feature of 2 of the reported cases. The results of the treatment of 3 patients exhibiting postural circulatory difficulties, 1 with Addison's disease and 2 without clinical adrenal insufficiency, by means of desoxycorticosterone acetate are presented.

NOTE.—Since the completion of this paper, a study of orthostatic hypotension by MacLean and Allen [31] has been published. They concluded that in the syndromes of primary orthostatic hypotension and orthostatic tachycardia, as well as in secondary orthostatic hypotension following extensive sympathectomy for essential hypertension, there is an inherent defect in the ability to return venous blood to the heart while the patient stands. They were able to improve significantly the ability of the circulation to adapt itself to the erect posture in some patients by the use of the tilted "head-up" bed. They suggest that this improvement in postural vascular adaptability coincides with an increase in circulating blood volume and a definite increase in the content of extracellular fluid in the lower extremities.

Dr. Arthur Fishberg made valuable suggestions; Dr. I. S. Wechsler gave us permission to include case 3 in this series, and Dr. George W. Thorn, of Johns Hopkins Hospital, furnished the pellets of desoxycorticosterone acetate used in case 1. The Ciba Pharmaceutical Products, Inc., supplied part of the desoxycorticosterone (percorten) used in this study.

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29. Gordon, E. S.: Use of Desoxycorticosterone and Its Esters in Addison's Disease, J. A. M. A. **114**:2549 (June 29) 1940.

30. Kuhlmann, D.; Ragan, C.; Ferrebee, J. W.; Atchley, D. W., and Loeb, R. F.: Toxic Effects of Desoxycorticosterone Esters in Dogs, Science **90**:496 (Nov. 24) 1939. Ragan, C.; Ferrebee, J. W.; Phyfe, P.; Atchley, D. W., and Loeb, R. F.: A Syndrome of Polydipsia and Polyuria Induced in Normal Animals by Desoxycorticosterone Acetate, Am. J. Physiol. **131**:73 (Nov.) 1940. Selye, H.: Compensatory Atrophy of the Adrenals, J. A. M. A. **115**:2246 (Dec. 28) 1940.

31. MacLean, A. R., and Allen, E. V.: Orthostatic Hypotension and Orthostatic Tachycardia: Treatment with the "Head Up" Bed, J. A. M. A. **115**:2162 (Dec. 21) 1940.

GOITER WITH ASSOCIATED MYASTHENIA GRAVIS

REPORT OF THREE CASES OF EXOPHTHALMIC GOITER AND ONE CASE OF ADENOMATOUS GOITER WITH HYPERTHYROIDISM

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Exophthalmic goiter with associated myasthenia is common, but exophthalmic goiter accompanied by myasthenia gravis of the bulbar type is rare. The first case of the association of these two diseases was reported by Rennie in 1908.[1] Ten additional cases of exophthalmic goiter and 1 case of adenomatous goiter with hyperthyroidism, all with myasthenia gravis, have been found recorded in the literature.[2] To this group we wish to add 3 more cases of exophthalmic goiter and 1 case of adenomatous goiter with hyperthyroidism combined with myasthenia gravis. In 1 of our cases subtotal thyroidectomy was performed successfully, with alleviation of symptoms of both diseases.

From the Division of Medicine (Drs. Kowallis and Haines) and the Division of Surgery (Dr. Pemberton), the Mayo Clinic.

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2. (*a*) Burger, W.: Ueber Thyreotoxikose mit spinalen Symptomen, Deutsches Arch. f. klin. Med. **162**:355-357, 1928. (*b*) Cohen, S. J., and King, F. H.: Relation Between Myasthenia Gravis and Exophthalmic Goiter, Arch. Neurol. & Psychiat. **28**:1338-1345 (Dec.) 1932. (*c*) Heuer, G. J.: The Cerebral Nerve Disturbances in Exophthalmic Goiter, Am. J. M. Sc. **151**:339-351 (March) 1916. (*d*) Rennie, G. E.: Myasthenia Gravis with Exophthalmic Goitre, Rev. Neurol. & Psychiat. **11**:475-478, 1913. (*e*) Schönberg, H.: Grenzfall von Morbus Basedowii und Myasthenia gravis pseudoparalytica, Deutsche med. Wchnschr. **63**:738-741 (May 7) 1937. (*f*) Schumacher and Roth: Thymektomie bei einem Fall von Morbus Basedowi mit Myasthenia, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **25**:746-765, 1913. (*g*) Sterling, W.: Maladie de Basedow, myasthénie et amyotrophie progressive, Rev. neurol. **1**:93-94 (Jan.) 1930. (*h*) Vedsmand, H.: Pluriglandular Insufficiency, Ugesk. f. læger **85**:405-407 (June 7) 1923. (*i*) Wolff, H. G.; Keutmann, H., and Cobb, S.: The Electromyogram in Myasthenia Gravis, Brain **51**:508-519 (Dec.) 1928. (*j*) Zondek, H.: Adynamischer Basedow, Schweiz. med. Wchnschr. **68**:65-68 (Jan. 15) 1938. (*k*) Allan, F. N.: Muscular Weakness and Hyperthyroidism, Myasthenia Gravis and Goitre, S. Clin. North America **14**: 1249-1255 (Oct.) 1934.

REPORT OF CASES

CASE 1.—A married woman aged 39 registered at the Mayo Clinic in November 1939. She complained of difficult speech of eleven days' duration and double vision of four days' duration. In 1933 her systolic blood pressure had been found to be as high as 168 mm. of mercury. In 1935 she had been noted to have prominent eyes. She was intolerant of heat. The presence of a goiter had been suspected, but it had not been verified. In June 1939 she had moved to another state and had been unable to adjust herself to her new environment but had become nervous and homesick. She had cried frequently and tired easily. In September 1939, because of nervousness and a basal metabolic rate of + 12 per cent, compound solution of iodine (Lugol's solution) had been prescribed, in a dosage of 5 drops taken three times daily, from which questionable benefit had been derived. In October 1939, about eleven days before she registered at the clinic, the patient had returned to her original home. During the excitement of her reception at home she had noted difficulty in speaking; the tongue seemed to be thick and awkward. The longer she talked, the more her words would slur, so that eventually she could not be understood. Rest restored her speech temporarily. About four days prior to her coming to the clinic she had been troubled with blurred and double vision; her face felt stiff and numb most of the time, and muscular weakness had become generalized. Eating was dreaded because of difficulty in swallowing. She was at her best in the morning. By afternoon she would be exhausted. She had lost little weight.

On physical examination the patient was found to have an expressionless face but a stimulated appearance which suggested exophthalmic goiter. The skin was warm and moist. There were some edema of the eyelids, with slight bilateral ptosis of the lids and exophthalmos, and evidence of slight weakness of the right inferior oblique and inferior rectus muscles. Tremor of the fingers was moderate. Weakness of the quadriceps muscles was slight. The thyroid gland was somewhat enlarged, each lobe being about 2.5 by 5.5 cm. in size, and was firmer than normal. A systolic bruit was heard over the right lobe. The uterus was nodular and enlarged to the level of the umbilicus. The systolic blood pressure was 140 to 148 and the diastolic pressure 84 to 90, expressed in millimeters of mercury. The pulse rate was 84 beats per minute. The basal metabolic rates were + 20 and + 21 per cent. The presence of an exophthalmic goiter was strongly suspected, and compound solution of iodine was administered. After seventeen days of iodine therapy, the patient's weakness was more marked, and she presented a picture of a person suffering from extreme exhaustion. In addition, she exhibited moderate bilateral ptosis of the eyelids and marked weakness of the quadriceps muscle. Basal metabolic rates were + 21 and + 23 per cent. The basal metabolic rate as subsequently determined in the hospital was + 10 per cent. The patient then received an intramuscular injection of 1 mg. of prostigmine methylsulfate. Within fifteen minutes a most dramatic change occurred. She said that she felt greatly improved. The double vision and ptosis vanished; the general muscular weakness and feeling of fatigue lessened, and the thick tongue and facial numbness disappeared. She could talk and smile with ease and could walk unassisted and with confidence. She relished her supper and ate it rapidly. This feeling of exhilaration lasted about three to four hours. The next day the patient received a subcutaneous injection of sterile water, without effect. Then the injection of 1 mg. of prostigmine methylsulfate was repeated, and again marked improvement followed. Consequently, the diagnosis of myasthenia gravis of the bulbar type was established. In spite of control of the symptoms and signs of myasthenia gravis, the patient continued to

show evidences of exophthalmic goiter, the most marked of which were edema of the eyelids, a warm, moist skin and fine tremor of the fingers. These signs, the increased size and firmness of the thyroid gland and the elevated basal metabolic rate made us feel that the diagnosis of exophthalmic goiter was almost certain. Treatment with compound solution of iodine, 10 drops administered three times daily; prostigmine bromide, 9 mg. administered orally five times daily, and aminoacetic acid, 5 Gm. administered three times daily, was continued, and the patient's condition improved markedly. In December double resection of the thyroid gland was performed. Eighteen grams of thyroid tissue was removed. The thymic area was explored, but thymus tissue was not found. Pathologic examination of the thyroid tissue removed showed multiple hyaline hemorrhagic degenerating fetal and colloid adenomas in a hypertrophic parenchymatous thyroid gland.

The postoperative convalescence of the patient was uneventful, and she was dismissed fifteen days after thyroidectomy. Her general condition at that time was definitely improved. She was instructed to take daily 10 drops of compound solution of iodine, 5 Gm. of aminoacetic acid and 15 mg. of prostigmine bromide.

In April 1940 the patient returned for reexamination and consideration of surgical operation for the uterine fibromyomas. She stated that prostigmine had been needed for only two weeks after she had returned home. She had continued to take compound solution of iodine and aminoacetic acid. Her condition subjectively and objectively was satisfactory. She had gained 17 pounds (8 Kg.). At this time she said that when she became tired, the sensation was more of physiologic exhaustion than of "paralysis." The basal metabolic rate was reported to be —5 per cent. A subcutaneous injection of 1 mg. of prostigmine methylsulfate did not produce any noticeable effect. Abdominal subtotal hysterectomy was performed. The postoperative convalescence of the patient again was uneventful, and she was dismissed eighteen days after operation and was instructed to continue to take 5 drops of compound solution of iodine daily but no other medication.

At the time of her last examination at the clinic, in November 1940, the patient was able to do her own housework. She did not have any true symptoms of myasthenia gravis. Results of a general examination were essentially negative except for an increase in weight and persistent mild hypertension. The basal metabolic rate was +2 per cent. She was dismissed with advice to reduce her weight and to continue to take compound solution of iodine for several years.

In March 1941 the patient reported by letter that her health was excellent. She had lost 20 pounds (9 Kg.) by restriction of her diet.

CASE 2.—The second patient was a married woman aged 56. She registered at the clinic in July 1938, complaining chiefly of difficulty in talking and swallowing of ten months' duration. For many years she had been afflicted with nervousness, palpitation, dyspnea and tremor. In about 1933 she had noted transient episodes of mild impairment of speech and occasional regurgitation of liquids. In September 1937 speech had become persistently more difficult, and her general course had been steadily downward. She said that her tongue "wouldn't work properly." The lower jaw had become so weak that if she did not support it, the mouth would remain open constantly. She had been unable to chew foods. Swallowing would produce episodes of choking. There was loss of appetite, with an associated decrease in weight of 35 to 40 pounds (16 to 18 Kg.). Ptosis of the eyelids had occurred, and general muscular weakness had become progressive. Her general condition had been somewhat better in the mornings, but frequent rest periods were of only temporary benefit.

Physical examination revealed a stimulated, emaciated woman. Her skin was warm and moist. Moderate ptosis of the eyelids was present. The mouth remained open, and saliva drooled from it. She experienced great difficulty in talking or swallowing. Virtually all the muscles of the body were atrophied in varying degree, and there was associated loss of strength. Her gait was a slow, unsteady shuffle. The thyroid gland was low lying, and palpable portions of each lobe measured 3 by 4 cm. The systolic blood pressure varied from 166 to 190 and the diastolic pressure from 108 to 140, expressed in millimeters of mercury. The pulse rate was 112 to 118 beats per minute.

Results of routine laboratory tests were normal save for elevated basal metabolic rates, + 62, + 49 and + 71 per cent. The favorable response of the patient to the intramuscular injection of 1 mg. of prostigmine methylsulfate was so definite that no doubt was left as to the validity of the diagnosis of myasthenia gravis. Because of the patient's history of nervousness, palpitation, dyspnea and tremor and because of the clinical picture of stimulation so characteristic of exophthalmic goiter, the enlarged thyroid gland and the elevated basal metabolic rates, the diagnosis of exophthalmic goiter was also made.

Compound solution of iodine was prescribed, 10 drops to be taken three times daily, with 3 mg. of prostigmine bromide to be taken orally five times daily. After seven days of this therapy, with rest in bed, the patient's general condition improved. She was able to talk and swallow much better than at the time of her admission. She could cough, sneeze and yawn. Another basal metabolic rate was + 49 per cent. Even though the patient exhibited some general improvement as a result of medical management, the surgical risk was still prohibitive. It was feared that she would be unable to cough up mucus or to swallow; hence, thyroidectomy was not done, but roentgen therapy was substituted. At the time of her dismissal, the patient was taking 10 drops of compound solution of iodine three times daily and 6 mg. of prostigmine bromide orally five times daily.

This patient never returned for further consideration. She died at home a few months after her dismissal from the clinic.

CASE 3.—The patient was a married woman aged 25. She registered at the clinic in March 1931. She complained chiefly of ptosis of the eyelids and double vision of one and a half year's duration and of difficulty in talking and swallowing of three months' duration. She always had been "warm blooded." In 1926 she had noticed that her legs trembled and that they seemed to be about to give way when she walked much. Only once had she actually fallen to her knees. Since 1929 she had been afflicted with transient episodes of diplopia and ptosis. In 1930, three months before she came to the clinic, she had experienced difficulty in swallowing both liquids and solid foods. Regurgitation had become more frequent; talking was an effort. Prolonged speech had tended to become thick and finally had failed. Diplopia and ptosis had occurred more often. General muscular weakness progressed, and at times the patient had fallen to the floor. Usually, she had felt well in the mornings but lost strength rapidly throughout the rest of the day. Rest periods had relieved her temporarily.

General examination revealed a well developed, obese woman, with masklike facies, marked bilateral ptosis of the eyelids and varying degrees of weakness of the ocular muscles. She appeared to be stimulated, and her skin was warm and moist. Moderately fine tremor of the hands was present. There was generalized muscular weakness, with moderate weakness of the quadriceps muscle. The thyroid gland was just palpable. The systolic blood pressure varied from 110 to 124 and

the diastolic pressure from 70 to 78, expressed in millimeters of mercury. The pulse rate varied from 89 to 98 beats per minute.

Results of laboratory investigations were normal save for elevated basal metabolic rates, + 22, + 23 and + 21 per cent. A diagnosis of myasthenia gravis was made on the basis of the history and the results of the general examination. The stimulated appearance and behavior of the patient, with the elevated basal metabolic rates, led to the suspicion of associated exophthalmic goiter.

In April 1931 administration of 10 drops of compound solution of iodine three times daily was commenced. After seven days of such therapy the basal metabolic rates had decreased to + 3 and + 5 per cent, and at the end of sixteen days, to — 4 per cent. The patient's general course was variable but tended to be worse. It was then decided to discontinue administration of compound solution of iodine and to start administration of ephedrine sulfate in doses of ⅔ grain (0.043 Gm.) twice daily.

By May 1931, a month later, the patient's general condition was definitely improved. She still tended to tire easily. Her hands were slightly tremulous. She was disturbed by palpitation. She had lost weight slightly; yet her appetite was good. Basal metabolic rates were +21 and +17 per cent. A second course of therapy with compound solution of iodine, 10 drops given three times daily, was ordered, in conjunction with administration of ⅔ grain (0.043 Gm.) of ephedrine sulfate twice daily. After nine days of this therapy the patient's general condition was further improved, both subjectively and objectively. The basal metabolic rate decreased from + 21 and + 17 per cent to + 3 and — 2 per cent. The diagnosis of exophthalmic goiter was thus verified and thyroidectomy was advised.

The patient did not return for operation, as had been planned. It was later learned from her husband that because of increased dysphagia she had choked to death suddenly in October 1931.

Case 4.—The patient was a married physician aged 56. He registered at the clinic in June 1935, complaining chiefly of loss of general strength and difficulty in chewing of six months' duration. The patient had felt perfectly well until January 1935, at which time he had noted that his power to chew definitely weakened after the first few bites of solid food. Such foods as meats had to be ground before he could eat them. He also had observed that his strength was normal in the mornings and that it gradually declined thereafter. Rest periods would revive him temporarily. In May 1935, three weeks before his admission to the clinic, dysphagia had occurred. He said that the "muscles of his throat didn't seem to contract" and that he had had to wash his food down with water. He thought his loss of 30 pounds (14 Kg.) of weight might have been caused by his fear of eating, for previously he had had a good appetite.

The general examination showed the patient to be normally developed but considerably overweight. He appeared to be stimulated, with skin that was warm and moist. He presented a fine type of hand tremor. The palpable portions of the thyroid gland were definitely nodular. The right lobe measured 4 by 6 cm. and the left 3 by 5 cm. Examination of the heart revealed a diastolic murmur characteristic of aortic insufficiency. The heart was of normal size and compensated. Marked sinus arrhythmia, verified by an electrocardiogram, was present. Loss of muscular strength was generalized and was of mild degree. The systolic blood pressure was 166 and the diastolic pressure was 80, expressed in millimeters of mercury. The pulse rate was 104 beats per minute.

The only positive laboratory observations were the elevated basal metabolic rates of + 19 and + 17 per cent and a roentgenologic shadow of undetermined

nature in the upper part of the mediastinum. A diagnosis of adenomatous goiter with hyperthyroidism was made, and myasthenia gravis was suspected.

The patient was instructed to take 10 drops of compound solution of iodine three times daily. In July 1935, one month later, he returned for reexamination. He thought he was slightly weaker than he had been at dismissal. Results of examination did not show any improvement in his condition. Administration of compound solution of iodine was discontinued, and ephedrine sulfate was prescribed, ⅛ grain (0.008 Gm.) three times daily. One level tablespoon of aminoacetic acid was to be taken five times daily. After five days of this regimen the patient could chew food more vigorously and strength returned to his arms and hands. Such a response to ephedrine sulfate substantiated the diagnosis of myasthenia gravis. At dismissal he was advised to continue to take ephedrine sulfate and aminoacetic acid.

In August 1935 reexamination showed the patient's general myasthenic state to be unchanged. Tremor of the hands had increased. The basal metabolic rate was found to be + 24 per cent. The only change in the therapeutic program was the addition of potassium chloride, 1 teaspoon three times daily. Thereafter the patient kept in constant contact with the clinic, either by personal presentation or by mail. His course was variable, with the general trend definitely downward. Different therapeutic agents, such as aminoacetic acid, ephedrine sulfate, prostigmine and potassium chloride, were employed, without much success.

In March 1937 the patient gave a history of angina pectoris. In May 1937 his condition was worse. He had been troubled by a cold, and the mucus produced distressed him. Swallowing was difficult. His heart "raced," and palpitation disturbed him. The carotid vessels were seen to pulsate strongly. Attention was focused on the thyroid gland, which was believed to be overactive again. All medication was stopped, and compound solution of iodine was prescribed, 15 drops three times daily for three or four days, at the end of which time 10 drops was to be taken three times daily. After seventeen days of iodine therapy the patient's general condition was considerably improved. His strength returned, and his nervousness decreased markedly. Pulsations of the carotid vessels diminished. The patient slept better. He was permitted to return home and was advised to take compound solution of iodine daily.

In September 1937 he presented himself for the last time. He had lost considerable weight. His loss of strength was more marked. His speech and his ability to swallow were poor. At times he could not retain food introduced by tube. His breathing was laborious. The administration of prostigmine bromide was started, and the dose was increased from 15 to 30 mg. daily, with no apparent effect.

In October 1937, after an attempt had been made to feed the patient by means of a tube, he suddenly collapsed. After the intramuscular injection of 1 mg. of prostigmine methylsulfate he regained consciousness. This dose was reenforced later by the oral administration of 15 mg. of prostigmine bromide. The patient improved so remarkably that he was able to swallow nourishment and take his feeding by tube without much difficulty that same day. He died suddenly three days later, while his wife was helping him with his morning toilet.

COMMENT

Exophthalmic goiter and myasthenia gravis may present symptoms that are somewhat similar, although as a rule when either condition exists the other can be readily excluded. Both may occur in any decade

of life; both affect females more frequently than males. Muscular weakness is a common symptom of both. Spontaneous exacerbation and remission, with a tendency toward progression, are characteristic of both diseases. Weakness of the ocular muscles frequently is seen in both conditions, but whereas ptosis of the lids is usual in myasthenia gravis, the upper lids are often retracted in exophthalmic goiter. In both diseases the thymus body may be abnormally enlarged, although the enlargement may not be exactly similar in the two diseases.

When the two diseases exist simultaneously either one may easily be overlooked. The response to prostigmine of patients who have myasthenia gravis is dramatic and is an important diagnostic point, since patients suffering from exophthalmic goiter alone are not benefited by it. The effect of iodine on exophthalmic goiter is well known, and it may be administered as an aid in diagnosis; however, in our cases its effect alone was not consistently good, and it may be that its characteristic effect on exophthalmic goiter might not be obtained for patients who also have untreated myasthenia gravis. The basal metabolic rate may afford important information, because it is not elevated in patients suffering from uncomplicated myasthenia gravis. Garvey,[3] in 1930, stated that the basal metabolic rate was less than normal in the presence of myasthenia gravis. He reported basal metabolic rates of — 23 and — 24 per cent in 1 case of myasthenia gravis and a rate of — 9 per cent in a second case. In a review of all the cases of myasthenia gravis on record at the Mayo Clinic, it was found that the basal metabolic rate had been determined in 40 cases and that in all it was within an acceptable normal range of — 18 to + 12 per cent. The basal metabolic rate was higher than + 10 per cent in 1 case and lower than — 10 per cent in 6 cases.

Pathologically, both exophthalmic goiter and myasthenia gravis are associated with significant involvement of the thymus body.[3a] The association of an enlarged thymus body with exophthalmic goiter was first recorded by Markham, in 1858. The incidence of a hyperplastic or hypertrophied thymus body in cases of exophthalmic goiter varies from 66 (Giordano[4]) to 100 per cent (Potter[5]). Other cited figures range between these extremes. In Giordano's survey of cases of adenomatous

3. Garvey, J. L.: Ophthalmoplegia and Graves' Disease, Ann. Int. Med. **3**:917-919 (March) 1930.

3a. Since this paper was written, the following important contribution has appeared: Blalock, A.; Harvey, A. M.; Ford, F. R., and Lilienthal, J. L.: The Treatment of Myasthenia Gravis by Removal of the Thymus Gland: Report of a Case, J. A. M. A. **117**:1529-1533 (Nov. 1) 1941.

4. Giordano, A. S.: The Frequency of Thymic Hyperplasia in Toxic and Non-Toxic Goiters, J. Indiana M. A. **16**:362-366 (Nov.) 1923.

5. Potter, E. B.: Persistent Thymus in Exophthalmic Goiter, in Stone, W. J.: Contributions to Medical Science Dedicated to Aldred Scott Warthin, Ann Arbor, Mich., George Wahr, 1927, pp. 205-220.

goiter with hyperthyroidism, the thymus body was found to be hyperplastic in 50 per cent of the cases, a figure which practically equals the incidence which he reported for exophthalmic goiter. Blackford and Freligh [6] studied carefully the observations made at necropsy on 74 patients suffering from exophthalmic goiter who had died in the course of the disease. They found a hypertrophic thymus body in all patients who were less than 40 years of age and in half of those who were more than 40 years of age. One of us (J. deJ. P.[7]) had the opportunity to study for a series of 7 patients suffering from exophthalmic goiter in whom hyperthyroidism had been completely controlled by partial resection the observations made at necropsy when death occurred, a year or more after partial thyroidectomy, from causes other than hyperthyroidism. Although the group was small, it appeared significant that in no case was a persistent or hypertrophic thymus body present. If it could be assumed that in some of these patients a hypertrophic thymus body had been present during the course of the hyperthyroidism, the absence of such hypertrophy after complete recovery of the patient would indicate that control of the hyperthyroidism had resulted in involution of the thymus body.

Weigert, cited by Norris,[8] in 1901, was the first to describe a thymic tumor associated with myasthenia gravis. Norris in 1937 brought to date his review of the literature of all cases of myasthenia gravis in which postmortem examination had been made. He found 82 such cases. In 37 cases, or 45 per cent, there were definite lesions of the thymus gland, in the nature either of hyperplasia or of a thymoma. Since 1937, 9 additional cases have been reported.[9] In 6 of these, lesions of the thymus body were present. The case reported by Schönberg was one of exophthalmic goiter and myasthenia gravis. Histopathologic examination of the thyroid tissue disclosed the presence of lymphocytosis and parenchymal changes "typical of Basedow's disease." Histopathologic examination of the thymus body revealed hyalinization of Hassall's

6. Blackford, J. M., and Freligh, W. P.: The Thymus in Adults with Especial Reference to Goiter, abstracted in Collected Papers of the Mayo Clinic, Philadelphia, W. B. Saunders Company, 1916, vol. 8, pp. 507-512.

7. Pemberton, J. deJ.: Recurring Exophthalmic Goiter, J. A. M. A. **94**:1483-1489 (May 10) 1930.

8. Norris, E. H.: A Thymoma (Adenoma of the Thymus) from an Unusual Case of Myasthenia Gravis, with Observations on the General Pathology, Am. J. Cancer **30**:308-317 (June) 1937.

9. Barton, F. E., and Branch, C. F.: Myasthenia Gravis: Report of a Case with Necropsy, J. A. M. A. **109**:2044-2048 (Dec. 18) 1937. Miller, H. G.: Myasthenia Gravis and the Thymus Gland, Arch. Path. **29**:212-219 (Feb.) 1940. Peer, G. F., and Farinacci, C. J.: Report of Case of Myasthenia Gravis Associated with Thymoma, Mil. Surgeon **82**:350-355 (April) 1938. Scannell, R. C.: Myasthenia Gravis: A Case with Necropsy, J. Iowa M. Soc. **30**:154-159 (April) 1940. Schönberg.[2e]

corpuscles, hyperemia and predominance of small round cells. Neither a thymic tumor nor thymic hyperplasia was distinctly present.

A review of the records of the Mayo Clinic revealed 8 cases of myasthenia gravis in which complete necropsy except for the brain and the spinal cord had been done. In 1 case examination of the thymus body had revealed nodular hyperplasia. In a second case a malignant thymoma was found, with metastasis to the left visceral and parietal pleuras. Including these 8 cases, the recorded number of cases of myasthenia gravis in which necropsy has been done now totals 99. In 45 cases, or approximately 45 per cent, prominent anatomic lesions of the thymus body were present. The significance of this relation remains unknown, but the incidence of it is far too high to be merely coincidental.

The physiologic chemistry underlying the state of exophthalmic goiter is still in the hypothetic stage, and the nature of the muscular weakness of this disease is unknown. Presumably it is due to intrinsic chemical and/or physical changes, some of which may in part involve the phosphocreatine mechanism. Because of the role of serum choline esterase in the conduction of nerve impulses, and to ascertain whether any possible relation to the muscular weakness present in exophthalmic goiter existed, values for serum choline esterase were determined in 13 cases in which exophthalmic goiter had been untreated. In all cases the values were normal.

At present the most favored theory concerning the cause of muscular weakness in myasthenia gravis suggests faulty transmission of nerve impulses due to a defect at the myoneural junction. The exact chemical reaction is not known. Whether there is excess choline esterase or inadequate acetylcholine at the motor end plates or curare-like toxin or some other unknown factor in the neuromuscular tissues remains to be determined. In cases of combined exophthalmic goiter and myasthenia gravis it may be that the goiter serves as the precipitator of the latter disease in the patient who has a latent tendency toward its development. The other possibility is that in rare instances exophthalmic goiter may produce muscular disturbances that are identical with those occurring in cases of myasthenia gravis. The infrequency of ptosis or of weakness of the pharyngeal muscles in cases of exophthalmic goiter with extreme generalized muscular weakness and the lack of effect of prostigmine on the muscular weakness associated with exophthalmic goiter argue against the latter possibility.

The prognosis in cases of properly treated exophthalmic goiter ordinarily is good, but in cases of myasthenia gravis it is grave, particularly if the bulbar type is present. When these two conditions prevail at the same time the prognosis is extremely poor. Yet it is of interest to note that spontaneous remission may occur in a patient who

has the combined syndromes. Rennie[10] reported a case of such recovery; the patient presented himself in a good state of health eleven years after the diagnosis had been made. It is also of interest to note that in our cases the clinical manifestations of hyperthyroidism preceded the onset of myasthenia gravis by months to years.

Surgical treatment of exophthalmic goiter complicated by myasthenia gravis offers certain difficulties. It is important that the patient be able to cough and to swallow in order to dispose of tracheal mucus, which often appears after thyroidectomy. In the instance herein recorded in which thyroidectomy was performed, treatment with prostigmine resulted in improvement in muscular strength sufficient for us to feel no concern in this regard. An ample supply of prostigmine for parenteral use was at hand, but in the absence of any unusual postoperative reaction it was not needed.

SUMMARY

Three cases of exophthalmic goiter combined with myasthenia gravis of the bulbar type and 1 case of adenomatous goiter with hyperthyroidism and myasthenia gravis have been presented. In 1 of these cases subtotal thyroidectomy has been performed successfully, with relief of symptoms of both conditions.

10. Rennie, G. E.: Exophthalmic Goitre Combined with Myasthenia Gravis, M. J. Australia **2**:416-417 (Nov. 15) 1919.

INTRAVENOUS USE OF SODIUM SULFADIAZINE IN THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA

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In previous papers we have reported on the behavior of sulfadiazine (2-[paraaminobenzenesulfonamido]-pyridine) in normal subjects,[1] and its use in the treatment of pneumococcic pneumonia.[2] Oral therapy with sulfadiazine [2] was supplemented with intravenous administration of the sodium salt of sulfadiazine in certain instances when rapid elevation of the level of the drug in the blood was desired. The behavior of the drug when given by vein suggested that administration of the entire dose of sulfadiazine by the intravenous route might be advantageous. Observations on the intravenous use of sodium sulfadiazine [3] without oral therapy in the treatment of pneumococcic pneumonia are described in the present paper.

MATERIAL AND METHOD

Intravenous Administration of Sodium Sulfadiazine to Normal Subjects.—As a guide to the therapeutic use of sodium sulfadiazine the fate of this compound administered by vein was first investigated in normal subjects (table 1). Five adult males with normal renal and hepatic function were each given 3 Gm. of sodium sulfadiazine (equivalent to 2.67 Gm. of sulfadiazine) intravenously as a

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* David Riesman Fellow in Medicine.

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1. Reinhold, J. G.; Flippin, H. F.; Schwartz, L., and Domm, A. H.: The Absorption, Distribution, and Excretion of 2-Sulfanilamido Pyrimidine (Sulfapyrimidine, Sulfadiazine) in Man, Am. J. M. Sc. **201**:106 (Jan.) 1941.

2. Flippin, H. F.; Rose, S. B.; Schwartz, L., and Domm, A. H.: Sulfadiazine and Sulfathiazole in the Treatment of Pneumococcic Pneumonia: A Progress Report on Two Hundred Cases, Am. J. M. Sc. **201**:585 (April) 1941.

3. Dr. Howard Hogan, Nepera Chemical Company, Yonkers, N. Y., provided the sodium sulfadiazine used in this study.

5 per cent solution in sterile distilled water. Doses averaged 0.038 Gm. per kilogram of body weight, ranging between 0.033 and 0.045 Gm. per kilogram. The concentration of the drug in the blood and urine was determined by the method of Bratton and Marshall.[4] The highest concentration of free drug observed in the blood was 15 mg. per hundred cubic centimeters fifteen minutes after injection. Blood collected eight hours after the drug was given showed an average concentration of 5.4 mg. of free sulfadiazine per hundred cubic centimeters, while after twenty-four hours an average concentration of 2.5 mg. per hundred cubic centimeters remained. Comparison with the response to intravenous injection of equivalent amounts of sodium sulfathiazole (the sodium salt of 2-[paraaminobenzenesulfonamido]-thiazole)[5] indicates that the concentration of sulfadiazine in the blood is much more effectively maintained.

The excretion of sulfadiazine in the urine was slower than that of sulfathiazole,[5] an average of 74 per cent of the former as compared with 96 per cent of the latter appearing in the urine within twenty-four hours. The equivalent of 93 per

TABLE 1.—*The Fate of a Single Intravenous Dose (3 Gm.) of Sodium Sulfadiazine*

	Blood *			Urine †			
Time, Hr.	Free Drug, Mg. per 100 Cc.	Total Drug, Mg. per 100 Cc.	Acetylated Drug, per Cent	Free Drug, Mg. per 100 Cc.	Total Drug, Mg. per 100 Cc.	Acetylated Drug, per Cent	Cumulative Excretion, per Cent
¼	11.6	12.8	10.0				
½	10.9	11.9	8.4				
1	9.5	10.5	9.5				
2	8.5	9.5	10.5				
4	6.9	8.1	14.8	115	147	22	17
8	5.4	6.4	15.6	64	101	36	35
24	2.5	3.5	28.6	48	91	47	74
48	0.8	1.6	50.0	31	50	39	93

* Average values for 5 subjects.
† Average values for 4 subjects.

cent of injected sulfadiazine was recovered in the urine within forty-eight hours. The figures for excretion are based on the assumption that all material reacting with the Bratton and Marshall reagent is unaltered drug or reacts as equivalent amounts of drug. The intravenous administration of a single 3 Gm. dose of sodium sulfadiazine did not result in any apparent untoward reaction. Our results agree with those of Peterson and associates.[6]

Treatment of Subjects with Pneumonia.—Twenty-five adult male patients with pneumonia, admitted consecutively, were treated with sodium sulfadiazine administered entirely by vein. As in previous studies, the diagnosis of pneumonia was established by clinical history, physical examination and, when indicated, by roentgenograms. A specific type of pneumococcus was obtained from the sputum or

4. Bratton, A. C., and Marshall, E. K., Jr.: A New Coupling Reagent for Sulfanilamide Determination, J. Biol. Chem. **128**:537 (May) 1939.

5. Reinhold, J. G.; Flippin, H. F., and Schwartz, L.: Observations on the Pharmacology and Toxicology of Sulfathiazole in Man, Am. J. M. Sc. **199**:393 (March) 1940.

6. Peterson, O. L.; Strauss, E.; Taylor, F. H. L., and Finland, M.: Absorption, Excretion, and Distribution of Sulfadiazine (2-Sulfanilamido-Pyrimidine), Am. J. M. Sc. **201**:357 (March) 1941.

the blood in all but 4 instances, and in these the pneumococci in the sputum failed to yield a type with pneumococcus serums types I to XXXIII. Repeated blood counts and daily urinalyses were made on all patients. Concentrations of free and total drug in the blood were determined for samples collected twelve hours after the preceding injection of the drug and immediately before the next injection. Other laboratory studies were performed as indicated.

Dosage of Sodium Sulfadiazine.—In order to make the conditions of this study as uniform as possible and to facilitate the collection of samples of blood and the administration of the drug, we employed the following routine: With the exception of the initial dose, sodium sulfadiazine was injected at 9 a. m. and 9 p. m. Patients admitted before 5 a. m. or 5 p. m. received the usual initial 2 to 3 Gm. dose of drug as soon as possible and were then placed on the routine dose schedule. Those admitted after 5 a. m. or 5 p. m. were given a somewhat larger initial dose (see next paragraph), depending on the time of admission, and were placed on the regular regimen twelve to sixteen hours later. Thus most of the patients received medication at the same time, day and night. Sodium sulfadiazine was administered intravenously as a 5 per cent solution in sterile distilled water, from a syringe equipped with a 21 gage needle. If a needle of this caliber is used there is little danger of introducing the solution too rapidly into the vein. Care was taken to avoid escape of the material into the tissues of the arm.

The first 8 patients in this study received an initial intravenous injection of 3 to 4 Gm. of sodium sulfadiazine, depending on the time of admission, followed by 3 Gm. every twelve hours, day and night. Treatment was continued until the temperature remained normal for thirty-six to forty-eight hours and there was evidence of clinical improvement. For the remaining 17 patients the same dose schedule was followed, except that smaller amounts (2 Gm.) of the drug were employed. The average total dose for patients receiving 3 Gm. was 26.5 Gm., as compared with 18 Gm. for those receiving the 2 Gm. dose. Of the 25 patients included in this report, 4 received type-specific serum in addition to the drug.

THERAPEUTIC RESULTS

In this report we have included every patient with a diagnosis of pneumonia who received drug therapy, regardless of complications or length of stay in the hospital. The relevant data concerning these patients are given in table 2. Of the 25 patients with pneumonia, 4 died. Cultures of blood from 7 (28 per cent) of the patients were positive for pneumococci; 3 of the 7 died. All of the patients who died represented extremely poor therapeutic risks. There is no significant difference in mortality rate with the use of smaller (2 Gm.) amounts of sodium sulfadiazine than with larger (3 Gm.) doses.

Influence of Treatment on Course of the Disease.—A critical drop in body temperature occurred in 14 patients within twenty-four hours and in 18 by the end of forty-eight hours. This agrees closely with the temperature response to oral therapy with sulfadiazine. The temperature fell and remained normal within twenty-four hours in only 2 instances and within forty-eight hours in 4 cases. In this respect the oral administration of sulfadiazine[2] gave more satisfactory results.

TABLE 2.—*Summary of Data for Twenty-Five Patients with Pneumococcic Pneumonia Treated with Sodium Sulfadiazine Administered Intravenously*

Patient	Age, Years	Treatment Begun, Day of Disease	Lobe Affected *	Type of Pneumococcus	Blood Culture	Sodium Sulfadiazine: Total Dose, Gm.	Sodium Sulfadiazine: No. of Injections	Type-Specific Antipneumococcus Serum, Units	Toxicity	Response	Comment
1	37	10	RL	IV	Negative	25	8	.....	Crystalluria	Good	
2	35	3	LL	VII	Negative	25	8	.....	.....	Good	
3	23	3	RL	I	Negative	31	10	.....	.....	Fair	Sterile pleural effusion
4	61	4	LU; LL	XXIX	Negative	24	8	.....	Crystalluria, occasional red blood cells	Good	Diabetes mellitus
5	39	2	LU	XIX	Negative	28	9	.....	Crystalluria, occasional red blood cells	Good	
6	72	4	RU; RM; RL	III	Positive	7	2	.....	.....	Death	Moribund on admission; no autopsy
7	62	6	RU; RL	...	Negative	28	9	.....	.....	Death	Degenerative heart disease with progressive failure; no autopsy
8	34	6	RU; RM; RL; LU; LL	IV	Positive	10	4	100,000	.....	Death	Leukopenia (white cell count 3,000) on admission; autopsy: lobar pneumonia involving all lobes
9	14	3	RL	XX	Negative	15	7	.....	Vomited once	Good	
10	33	6	RU; RM; RL	XIV	Negative	26	13	240,000	Psychosis	Fair	
11	49	2	RL	III	Negative	17	8	.....	Vomited once	Good	
12	29	1	RL	I	Negative	18	8	.....	.....	Good	
13	72	2	RL	III	Positive	24	11	400,000	.....	Fair	
14	22	2	RL	XII	Negative	19	9	.....	.....	Good	
15	34	6	RU	VIII	Positive	18	8	.....	.....	Good	
16	48	7	LU; LL	...	Negative	13	6	.....	.....	Good	
17	34	4	RM; RL	...	Negative	20	9	.....	.....	Good	
18	38	2	RL	V	Positive	18	8	.....	.....	Good	
19	40	2	RL	...	Negative	22	10	.....	Crystalluria	Good	Acute alcoholism
20	43	2	LL	I	Negative	14	6	.....	.....	Good	
21	39	3	LL	XI	Negative	22	10	.....	.....	Fair	
22	45	2	RL	VIII	Positive	18	8	.....	.....	Good	
23	55	10	RU	I	Positive	20	9	500,000	.....	Death	Autopsy: lobar pneumonia involving upper lobe of right lung, acute bacterial endocarditis
24	28	4	RU; RM	VIII	Negative	16	7	.....	.....	Good	
25	68	3	RL; LL	II	Negative	19	9	.....	.....	Good	

* The affected lobes of the lungs are designated by the following abbreviations: RU, upper lobe of the right lung; RM, middle lobe of the right lung; RL, lower lobe of the right lung; LU, upper lobe of the left lung, and LL, lower lobe of the left lung.

However, it should be pointed out that in this series the persisting elevation in temperature, following the critical fall, represented a low grade fever (99 to 100 F). A return to normal temperature within forty-eight hours has constituted one of the outstanding features of therapy with sulfanilamide or one of its derivatives in cases of pneumonia but is actually less important than the improvement in the patient's general condition. As shown in table 2, the therapeutic response in those patients who recovered was designated as good or fair. For 17 patients the results were good, and for 4 they were fair. There was no difference in temperature or therapeutic response of patients receiving 3 Gm. or those receiving 2 Gm. doses of the drug.

Complications.—The number of patients in this series is too small to permit evaluation of the incidence or significance of complications (table 2). Individual cases of massive pleural effusion and acute bacterial endocarditis constituted the only complications observed.

Toxicity.—The toxic reactions encountered in the course of this study are shown in table 2. Vomiting occurred in 2 cases but only once in each. In 1, vomiting followed immediately the injection of the drug, and this we believe was due to too rapid administration through an 18 gage needle. The other patient vomited on the third day of treatment after a rather large meal. The low incidence of vomiting in this series is comparable to that observed with the oral administration of sulfadiazine in the treatment of pneumonia.[2]

Crystals in small numbers, presumably of sulfadiazine, were observed in the urine of 4 patients. In 2 instances the crystals were accompanied by red blood cells, also in small numbers. A single patient showed definite evidence of a psychosis, which may have been caused by the drug.

Blood Levels.—Past experience with the use of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine [7]) and sulfathiazole [8] has failed to show any definite correlation between the therapeutic effectiveness of these drugs and the concentration of free drug in the blood. Therefore, the schedule of doses which we have employed in this study is empiric. Experience with sulfadiazine and other derivatives of sulfanilamide indicates that a blood level of free sulfadiazine of 5 mg. per hundred cubic centimeters is therapeutically effective in the treatment of pneumonia. Future work may show that lower concentrations are

7. Flippin, H. F.; Lockwood, J. S.; Pepper, D. S., and Schwartz, L.: The Treatment of Pneumococcic Pneumonia with Sulfapyridine, J. A. M. A. **112**: 529 (Feb. 11) 1939.

8. Flippin, H. F.; Reinhold, J. G., and Schwartz, L.: Sulfapyridine and Sulfathiazole Therapy in Pneumococcic Pneumonia, J. A. M. A. **116**:683 (Feb. 22) 1941.

equally effective. As indicated in table 3, an average blood level of free sulfadiazine of 11 mg. per hundred cubic centimeters was obtained when 3 Gm. of sodium sulfadiazine was administered intravenously every twelve hours. In the blood of those patients receiving 2 Gm. doses, the average concentration of free drug was 6.1 mg. per hundred cubic centimeters. The lowest average level observed with the smaller dose at any one time was 4.8 mg. per hundred cubic centimeters, and this was reached twelve hours after the last injection; so the 2 Gm. dose is sufficient for effective treatment of pneumonia. In this connection it is of interest to note that the blood levels are consistently higher during the height of illness than during the last two days of therapy. This, we believe, is a result of the impaired renal function caused by

TABLE 3.—*Effect of Repeated Intravenous Administration of Sodium Sulfadiazine* *

	3 Gm. Every 12 Hr.†			2 Gm. Every 12 Hr.‡		
Dose	Free Drug, Mg. per 100 Cc.	Total Drug, Mg. per 100 Cc.	Acetylated Drug, per Cent	Free Drug, Mg. per 100 Cc.	Total Drug, Mg. per 100 Cc.	Acetylated Drug, per Cent
2	8.8	10.1	12.9	7.5	8.6	12.8
3	10.1	11.6	12.9	7.7	8.7	11.5
4	11.5	12.8	10.1	6.8	7.9	13.9
5	13.3	14.9	10.7	6.2	7.1	12.7
6	12.7	13.9	8.6	6.0	6.7	10.4
7	12.1	13.4	9.7	5.3	6.0	11.7
8	10.9	12.1	9.9	5.5	6.2	11.3
9	8.6	9.9	13.1	5.0	5.9	15.2
10	...	...	....	4.8	5.4	11.1
Average	11.0	12.3	10.6	6.1	6.9	11.6

* A sample of blood was collected twelve hours after each dose.
† Average values for 8 patients.
‡ Average values for 17 patients.

the infectious process before it has been brought under control of the drug. Studies on urinary output and nitrogen retention [8] lend support to this view. Concentration of acetylsulfadiazine remained low.

COMMENT

Sodium sulfadiazine administered intravenously is an effective therapeutic agent in the treatment of pneumonia and may be used with a satisfactory margin of safety to the patient. This form of therapy is offered not as a routine procedure but as a method of treatment which may be resorted to in cases in which oral therapy is impracticable or impossible. Further experience may show that smaller doses or longer intervals between injections may be substituted for those employed in this study without sacrifice of therapeutic effectiveness.

SUMMARY

In normal subjects 3 Gm. of sodium sulfadiazine administered by vein maintained an average concentration of free drug in the blood above 5 mg. per hundred cubic centimeters for eight hours. In patients with pneumonia 2 Gm. at twelve hour intervals maintained an average concentration above 5 mg. per hundred cubic centimeters, while 3 Gm. maintained an average concentration above 8 mg. per hundred cubic centimeters.

Sodium sulfadiazine administered by vein at twelve hour intervals is an effective method for treatment of pneumococcic pneumonia. Results are comparable to those obtained by oral therapy with sulfadiazine.

Administration of sodium sulfadiazine by vein appears to be a safe procedure.

Technical assistance was given by Miss Shlomith Bethlahmy and Miss Beatrice Doak, who were detailed for this and related studies on pneumonia by the Pennsylvania State Department of Health, Division of Pneumonia Control.

INFECTIOUS NEURONITIS

REVIEW OF LITERATURE AND PRESENTATION OF FOUR CASES

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Since the first World War an apparently infectious form of generalized neuronitis has come to be recognized as a distinct clinical entity. It is characterized by an ascending paralysis which usually begins in the lower limbs and often involves the facial muscles, by a normal cell count and an increase in protein in the spinal fluid and by complete recovery in a large proportion of cases. A description which probably applies to this disease was given by Osler,[1] in 1892, under the name of "acute febrile polyneuritis." Guillain, Barré and Strohl,[2] in 1916, described a series of cases, and the term Guillain-Barré syndrome has been used by many writers since that time. Other terms which have been used are polyradiculoneuritis,[3] infective polyneuritis,[4] infective neuronitis,[5] radiculoneuritis with acellular hyperalbuminosis of the cerebrospinal fluid [6] and acute benign infectious myelitis.[7]

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1. Osler, W.: Principles and Practice of Medicine, New York, D. Appleton and Company, 1892, p. 777.

2. Guillain, G.; Barré, J. A., and Strohl, A.: Sur un syndrome de radiculonévrite avec hyperalbuminose du liquide céphalorachidien sans réaction cellulaire, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1462 (Oct. 13) 1916.

3. (*a*) Barker, L. F.: Acute Diffuse (Cerebral and Spinal) Polyradiculoneuritis Following Oral Sepsis, Arch. Neurol. & Psychiat. **31**:837 (April) 1934. (*b*) Madigan, P. S., and Marietta, S. U.: Polyradiculoneuritis, Ann. Int. Med. **12**:719 (Nov.) 1938. (*c*) Stone, T., and Aldrich, K.: Acute Polyradiculoneuritis, J. A. M. A. **114**:2196 (June 1) 1940.

4. (*a*) Bradford, J. R.; Bashford, E. F., and Wilson, J. A.: Acute Infective Polyneuritis, Quart. J. Med. **12**:88 (Oct.) 1918. (*b*) Pinckney, C.: Acute Infective Polyneuritis, Brit. M. J. **2**:333 (Aug. 15) 1936.

5. (*a*) Jacobi, H. G.: Infective Neuronitis, Arch. Int. Med. **48**:764 (Nov., pt. 1) 1931. (*b*) Kennedy, F.: Infective Neuronitis, Arch. Neurol. & Psychiat. **2**:621 (Dec.) 1919. (*c*) McIntyre, H. D.: Infective Neuronitis, Ohio State M. J. **33**:815 (Aug.) 1937.

6. Guillain, G.: Radiculoneuritis with Acellular Hyperalbuminosis of the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **36**:975 (Nov.) 1936.

7. Sands, I. J.: Acute Benign Infectious Myelitis, J. A. M. A. **96**:23 (Jan. 3) 1931.

The term neuritis has been defined by Cobb and Coggeshall [8] as a "degenerative (often inflammatory) process in any part of the peripheral neuron." It has thus been used as a general term, covering involvement of the nerve cell, nerve root or peripheral process. Inasmuch as the cell body or the peripheral process is seldom involved alone, without some effect on the other, it may be more accurate to use the term neuronitis, introduced by Mills [9] to designate involvement of the entire neuron.

ETIOLOGY

In his early description, Osler remarked that the onset of this disease resembles that of an acute infectious disease. Certainly the frequency with which general symptoms precede the attack is strongly suggestive of an infectious etiologic agent. In 49 of the 122 cases in the literature reviewed here there was a history of preceding illness, such as coryza, aches and pains and gastrointestinal disturbance. In all 4 of the cases reported here the patients told of antecedent infection of the upper respiratory tract or general aches and pains.

The etiologic agent has not been identified but is generally thought to be a virus. Cobb and Coggeshall [8] stated that in the few cases in which necropsy has been done the changes in the central nervous system have suggested a virus as the etiologic agent.

In about 70 per cent of the cases the disease has occurred in persons between the ages of 20 and 50 years, but extremes of age have been reported. About 25 per cent of patients have been under 20 and 5 per cent over 50 years. The ages of the patients in our own series were 16, 20, 50 and 52 years. In the reported cases in which sex was mentioned, approximately 60 per cent of the patients were male. In the cases reported here, 2 patients were male and 2 were female.

CLINICAL COURSE

As already pointed out, the onset is often attended by coryza, aches and pains and gastrointestinal disturbances. Of the cases reviewed, such preceding illness was recorded for 31 per cent; in the remainder, the disease was first evidenced in most cases by motor symptoms, including paralysis of the extremities, loss of sphincter control and disturbance of reflexes. Sensory disturbances were experienced in approximately 50 per cent of cases.

Table 1 lists some of the commonest clinical findings in the cases reviewed. One must bear in mind that many authors were not definite in their presentation of symptoms and findings.

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8. Cobb, S., and Coggeshall, H. C.: Neuritis, J. A. M. A. **103**:1608 (Nov. 24) 1934.

9. Mills, C. K.: The Reclassification of Some Organic Nervous Diseases on the Basis of the Neuron, J. A. M. A. **31**:11 (July 2) 1898.

TABLE 1.—*Clinical Findings and Mortality**

Author	Number of Cases	Previous Illness	Fever	Facial Paralysis	Palsy of Other Cranial Nerves	Paralysis of Sphincters	Paralysis of Extremities	Loss of Deep Reflexes	Loss of Abdominal Reflexes	Sensory Disturbance	Number of Deaths
Barker [2a]	1	0	1	1	1	0	1	Diminished	0	1	0
Bradford, Bashford and Wilson [4a]	30	?	?	?	?	?	?	?	?	?	8
Casamajor [1c]	2	1	1	1	0	0	2	1	1	0	2
Casamajor, L., and Alpert, G. R.: Am. J. Dis. Child. **61**: 99 (Jan.) 1941	3	1	1	1	0	0	3	3	?	1	0
Fox and O'Connor (present series)	4	3	0	1	0	1	4	4	2	2	1
Gilpin, Moersch and Kernohan [13]	20	13	0	7	0	0	0	18	20	15	5
Guillain [6]	10	0	0	2	1	2	7	8	10	10	0
Holmes [12]	12	?	?	?	?	?	?	?	?	?	2
Kennedy [5b]	4	4	3	4	2	3	3	3	1	2	1
Madigan and Marietta [3b]	1	0	1	1	1	0	1	1	1	1	0
McIntyre [5c]	7	2	0	5	4	2	4	5	5	6	2
Pinckney [4b]	5	3	0	2	3	1	2	3	4	2	1
Strauss, I., and Rabiner, A.: Arch. Neurol. & Psychiat. **23**: 240 (Feb.) 1930	7	4	2	0	1	3	4	4	4	6	0
Stone and Aldrich [2c]	2	1	0	2	1	0	2	1	1	2	0
Taylor, E. W., and McDonald, C. A.: Arch. Neurol. & Psychiat. **27**: 79 (Jan.) 1932	16	8	3	16	3	5	5	11	10	12	3
Viets, H. R.: Arch. Neurol. & Psychiat. **17**: 794 (June) 1927	2	1	1	1	0	1	1	2	1	2	1
Totals	126	41	13	42	17	18	39	65	60	62	26

* It should be noted that except for the numbers of cases and numbers of deaths, data for the series of Bradford and associates and of Holmes (a total of 42 cases) are not included in this table.

Disturbances of motor function are the most striking evidence of the disease. Fatigue and muscular weakness, most pronounced in the extremities, are frequently present in the early stage. A few patients show no such preliminary weakness but pass directly into the paralytic phase: A patient may suddenly find himself unable to rise from a sitting position or may begin to stumble as he walks. The affected muscles are flaccid but seldom show wasting. According to Pinckney,[4b] reflexes are sometimes surprisingly obtained when voluntary power is almost absent. Pinckney also stated that the paralysis is sometimes greater in the proximal than in the peripheral portions of the limbs. The paralysis usually involves both sides, though not necessarily equally. The upper limbs are usually involved after the lower. The intercostal muscles and the diaphragm are seldom involved. As shown in table 1, abdominal and deep reflexes are abolished in about 50 per cent of the cases. This is usually noticeable in the early stages of the disease and is sometimes the only evidence of nerve damage. In about 35 per cent of the cases facial paralysis is apparent; when it occurs, it follows paralysis of the limbs. In 13 per cent of the cases other cranial nerves are involved; palsies of the cranial nerves appear as diplopia, nystagmus, lingual deviation, dysphagia and aphasia.

Sensory disturbances are neither constant nor characteristic. In about 50 per cent of the cases the patients complained of sudden pain, paresthesia or anesthesia.

The prognosis in this disease is usually good. As indicated in table 1, the mortality in the literature reviewed was approximately 20 per cent; it should be noted that in 10 cases death occurred in wartime, when other hazards may have been somewhat greater than those encountered in civilian practice. The paralysis in the survivors commonly disappeared within two or three months; in 3 of our cases paralysis disappeared within a few days. Bradford and associates [4a] stated that six months' convalescence was usually necessary before a patient could return to his duties. The process of recovery occurs in opposite order from that of development of paralysis; i. e., the arms usually regain their normal tonus before the legs. It has been noted in a few cases that deep tendon reflexes were slow in returning and have occasionally been absent for years after apparent recovery from the disease.

LABORATORY FINDINGS

Blood studies offer little of significance in cases of this disease. According to Bradford and co-workers, there may be a moderate leukocytosis, but total red cell, total white cell and differential counts are normal. Examination of cerebrospinal fluid is of the greatest importance; the significant findings are a marked elevation of protein and a normal number (or total absence) of cells. This is the so-called albu-

minocytologic dissociation. Guillain stated that unless the cerebrospinal fluid protein exceeds 300 mg. per hundred cubic centimeters, a case does not belong to this syndrome.

The results of examinations of cerebrospinal fluid recorded in the literature reviewed here are shown in table 2. In 55 cases (made up largely of the wartime groups of Bradford and associates, Holmes and Kennedy), spinal fluid protein was not mentioned. Among the others, however, significant increase in protein was observed in 56 cases. In 85 cases the cell count was within normal limits; in 25 cases this important point was not mentioned.

TABLE 2.—*Results of Examination of Spinal Fluid*

	Number of Cases	Number of Instances of Normal Cells	Number of Instances of Increased Protein
Barker [2a]	1	1	1
Bradford, Bashford and Wilson [4a]	30	30	?
Casamajor [10]	2	?	?
Fox and O'Connor (present series)	4	4	4
Gilpin, Moersch and Kernohan [13]	20	18	20
Guillain [6]	10	10	9
Holmes [12]	12	?	?
Kennedy [5b]	4	?	?
Madigan and Marietta [5b]	1	1	1
McIntyre [5c]	7	7	7
Pinckney [4b]	5	4	4
Strauss, I., and Rabiner, A.: Arch. Neurol. & Psychiat. **23**: 240 (Feb.) 1930	7	?	?
Taylor, E. W., and McDonald, O. A.: Arch. Neurol. & Psychiat. **27**: 79 (Jan.) 1932	16	4	4
Viets, H. R.: Arch. Neurol. & Psychiat. **17**: 794 (June) 1927	2	1	1
Casamajor, L., and Alpert, G. R.: Am. J. Dis. Child. **61**: 99 (Jan.) 1941	3	3	3
Stone and Aldrich [3c]	2	2	2
Totals	126	85	56

Stone and Aldrich [3c] pointed out that the elevation of protein may not be apparent at the first examination; in 1 of their cases it was first observed on the seventh day of the disease and in another on the fourteenth day. Once hyperalbuminosis of the cerebrospinal fluid develops, it is likely to persist through convalescence.

DIFFERENTIAL DIAGNOSIS

It is important, of course, to differentiate this disease from poliomyelitis. Albuminocytologic dissociation may occur rarely in cases of poliomyelitis, but the protein is not likely to reach the high levels encountered in cases of infectious neuronitis. If the paralysis involves the intercostal muscles, the disease is probably not infectious neuronitis.

Postdiphtheritic polyneuritis may cause a similar increase in cerebrospinal fluid protein but may usually be identified by smears and cultures

of nose and throat. Syphilis may occasionally give rise to acellular hyperalbuminosis, but it may be recognized by the history and by the positive Wasserman reaction of the blood or the spinal fluid.

Muscular atrophies and dystrophies do not usually cause any abnormality of the cerebrospinal fluid; in instances in which the protein is elevated, it seldom exceeds 100 mg. per hundred cubic centimeters. Tumor of the spinal cord may be recognized by altered pressure relations and frequently by localizing sensory and motor changes.

Alcoholic neuritis is usually accompanied by edema and vasomotor symptoms; in cases of such disease, moreover, the patients have a history of alcoholism and faulty diet. Lead neuritis is usually associated with severe gastrointestinal symptoms and shows a localization of motor disturbance in the extensor muscles of the hand and forearm.

PATHOLOGY

Inasmuch as fatalities in cases of this disease have been relatively few, pathologic investigation has not been extensive. In gross examination of specimens in 6 cases of fatal infectious neuronitis Bradford, Bashford and Wilson [48] found edema of the brain and the spinal cord and a few petechial hemorrhages. Microscopically, they found degeneration of the cells of the anterior and posterior horns. In the peripheral nerves there were wallerian degeneration and proliferation of cells about the sheath of Schwann; these changes were more marked in motor than in sensory nerves and more pronounced in nerves of the lower than in those of the upper extremities. Casamajor [10] noted an increase of cellular neuroglia in the central gray matter, around root fibers and in the posterior root ganglions.

Gilpin, Moersch and Kernohan [11] studied 3 cases in which they found degenerative changes limited to the peripheral nerves. They observed proliferation of the cells of the sheath of Schwann, patchy destruction of the myelin sheaths and active degeneration of the axis-cylinders; there was marked edema of the supporting tissues. Holmes [12] reported similar changes in 2 fatal cases.

REPORT OF CASES

Case 1.—A man aged 20 first became ill eleven days before admission to the hospital, at which time he had an infection of the upper respiratory tract and complained of some dizziness. During the following week he had pain in his knees, ankles and right wrist and was irritable. Four days before admission he had beginning paralysis of the legs.

10. Casamajor, L.: Acute Ascending Paralysis Among Troops: Pathologic Findings, Arch. Neurol. & Psychiat. **2**:605 (Dec.) 1919.

11. Gilpin, S. F.; Moersch, F. P., and Kernohan, J. W.: Polyneuritis (a Group Referred to as Neuronitis), Arch. Neurol. & Psychiat. **35**:937 (May) 1936.

12. Holmes, G.: Acute Febrile Polyneuritis, Brit. M. J. **2**:37 (July 14) 1917.

Physical Examination.—The man was well developed, apparently well nourished and in good spirits. He was unable to sit up in bed or flex his knees, ankles or right wrist. There were hyperesthesia and pain over the right wrist and partial flaccid paralysis of the flexor muscles of the knees, thighs and arms. The reflexes were all active except the achilles, which was absent. The pharynx was injected. The chest and abdomen were normal. The temperature at admission was 100 F.

Laboratory Findings.—Leukocytes numbered 10,500 per cubic millimeter. A differential count showed 75 per cent polymorphonuclear cells, 21 per cent lymphocytes, 3 per cent monocytes and 1 per cent basophils. The urine was normal. The spinal fluid showed 5 cells per cubic millimeter, 332 mg. of protein, 712 mg. of chlorides and 85 mg. of sugar per hundred cubic centimeters and a negative Kahn reaction.

Course of Illness.—The temperature rose to 101.4 F. on the second day of hospitalization but declined to normal on the fifth day. Treatment was symptomatic, and the patient's condition gradually improved. On the sixth day after his admission, his paralysis had greatly subsided and there was no muscle tenderness; he was then permitted to go to his home, where he recovered completely from his paralysis.

Case 2.—A girl aged 16 first became ill eleven days before admission to the hospital, when she began to complain of generalized aches and pains and tingling sensations in her toes and fingers. There was no fever, cough or coryza. Three days before admission she began to lose the use of her lower extremities, and a noticeable weakness began to develop in her upper extremities. The condition became worse, with progressive paralysis of the lower extremities and the onset of pain in the lumbar portion of the back.

Physical Examination.—The patient was well developed and apparently well nourished. She lay quietly in bed, unable to raise her lower extremities. Her face was flushed, and there was beginning paralysis on the right side of the face. She was able to move her arms only slightly. There was no rigidity of the neck. The tongue was red and the pharynx injected. The chest and abdomen were normal. The strength of the grasp was diminished in both hands. The extensor muscles of the arms and the flexor muscles of the legs were exceedingly weak; the flexor muscles of the arms and the extensor muscles of the legs were only slightly stronger. The biceps reflexes were diminished; the triceps, patellar and achilles reflexes were absent. Babinski and Kernig signs could not be elicited. Position sense was diminished in the lower extremities, but sensations were otherwise normal.

Progress.—The patient remained in the hospital for only two days, during which time the diagnosis of infectious neuronitis was made. During this time the temperature remained normal and the treatment was symptomatic. At the time she was discharged to her home her condition was essentially unchanged except that the paralysis was slightly increased. In the first week at home the patient began to regain some muscular function, and by the end of four weeks the paralysis had disappeared entirely.

Laboratory Findings.—The leukocyte count at admission was 11,500 per cubic millimeter. The hemoglobin concentration was 80 per cent. The spinal fluid contained 6 cells per cubic millimeter and 365 mg. of protein, 743 mg. of chlorides and 40 mg. of sugar per hundred cubic centimeters. No organisms could be demonstrated in the spinal fluid by smear or culture.

CASE 3.—A man aged 50 had a sore throat lasting eight days about four weeks before admission to the hospital. The day after recovery from his sore throat, he noticed a tingling sensation in his toes and a sense of numbness from his waist down. Two days later a steppage gait developed. The severity of the symptoms increased until it was impossible to walk. The previous medical history added nothing of significance.

Physical Examination.—The patient was well developed, evidently well nourished and not in apparent discomfort. The pupils were both slightly irregular and reacted sluggishly to light and distance. The pharynx was slightly injected. The chest was normal. The upper extremities were normal. There was no muscle or tendon tenderness of the lower extremities, and the paralysis apparently had disappeared entirely. There was loss of vibratory sense in the lower extremities, pelvis and spine up to the fifth thoracic vertebra. The senses of pain, light touch and temperature were not impaired. Tendon, abdominal and cremasteric reflexes were absent. The Babinski reaction could not be elicited; the gait had a slight steppage quality.

Progress.—The patient was in the hospital only three days, until the diagnosis of infectious neuronitis had been established. During this time he had no fever, and his symptoms remained unchanged. He was able to walk out of the hospital, and his steppage gait disappeared in the following month.

Laboratory Findings.—At the time of the patient's admission to the hospital the urine was normal. The red cell count was 4,980,000 and the leukocyte count 8,150 per cubic millimeter. The differential count was normal. The Wassermann and Kline reactions were negative. The blood contained 29 mg. of nonprotein nitrogen and 5.8 Gm. of total protein per hundred cubic centimeters, and the albumin-globulin ratio was 3.2:2. The spinal fluid showed 3 cells per cubic millimeter and 660 mg. of protein per hundred cubic centimeters. The Wassermann and Kline reactions of the spinal fluid were negative, as were cultures and smears for organisms. The spinal fluid contained 92 mg. of sugar and 686 mg. of chlorides per hundred cubic centimeters. Roentgenograms of the dorsal and lumbar portions of the spine were essentially normal.

CASE 4.—A woman aged 52 became ill on Jan. 22, 1941, with severe cramplike pains all over her body, headache and backache. She did not experience nausea or vomiting, and there was no history of chills or fever.

Physical Examination.—On January 23 the pharynx was slightly injected, and the chest and abdomen were normal. There was muscle tenderness in both legs but no rigidity. The tendon reflexes were diminished.

Progress.—The patient was given the usual treatment for grip. On January 26 severe pains, numbness and flaccid paralysis occurred in both legs, and the reflexes of the legs and abdomen were completely absent. On January 27 the patient was transferred to a hospital, and one of us (M. J. F.) was called in consultation; on the same day palsy of the right side of the face became apparent, as well as paralysis of the urethral and rectal sphincters. On January 30 both arms began to show some weakness. During the following week there was no further progression of paralysis, but extensive bronchopneumonia developed, which did not respond to treatment. The patient died on February 5. Unfortunately permission for autopsy was refused.

Laboratory Findings.—Examination of the spinal fluid on January 27 showed 1 cell per cubic millimeter and a total protein content of 156 mg. per hundred

cubic centimeters. It contained 731 mg. of chlorides and 88 mg. of sugar per hundred cubic centimeters, and the Kolmer reaction was negative.

COMMENT

The first 3 cases presented here demonstrate the favorable progress and complete recovery seen in a large proportion of the cases of infectious neuronitis. It would have been enlightening to ascertain the extent and the exact nature of the complications in case 4 through an autopsy.

SUMMARY

1. The literature on infectious neuronitis is reviewed.

2. The syndrome is characterized as follows: Previous illness occurs in about 50 per cent of the cases, with an associated ascending paralysis; acellular hyperalbuminosis of the spinal fluid is of great importance in establishing a diagnosis. The facial nerve is involved in about 35 per cent of the cases, and sensory changes may or may not be present.

3. Four cases of this disease, with a satisfactory recovery in 3, are described. In the fourth case the patient died of complicating bronchopneumonia; permission for autopsy was refused.

SERUM PROTEINS IN CIRRHOSIS OF THE LIVER

I. RELATION TO PROGNOSIS AND TO FORMATION OF ASCITES

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Filinski [1] reported that in diseases of the liver, such as cirrhosis, catarrhal jaundice, amyloidosis and carcinomatosis from primary carcinoma of the bile duct, the albumin-globulin ratio of the serum was reversed. He concluded that the alterations in serum protein values were due to pathologic changes in the liver. In many subsequent reports containing single observations on the serum proteins of patients with cirrhosis of the liver, authors [2] agreed that the albumin-globulin

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1. Filinski, W.: L'augmentation du taux de la globuline dans le sérum du sang comme résultat de l'insuffisance hépatique, Presse méd. **30**:236, 1922.

2. (*a*) Salvesen, H. A.: Variations in Plasma Proteins in Nonrenal Conditions, Acta med. Scandinav. **72**:113, 1929. (*b*) Abrami, P., and Wallich, R.: Modifications du sérum sanguin du foie avec ascites: Inversion du rapport sérines-globulines, Compt. rehd. Soc. de biol. **101**:291, 1929. (*c*) Wiener, H. J., and Wiener, R. E.: Plasma Proteins, Arch. Int. Med. **46**:236 (Aug.) 1930. (*d*) Peters, J. P., and Eisenman, A. J.: The Serum Proteins in Diseases Not Primarily Affecting the Cardiovascular System or Kidneys, Am. J. M. Sc. **186**:808, 1933. (*e*) Snell, A. M.: The Effects of Chronic Disease of the Liver on the Composition and Physiochemical Properties of Blood: Changes in the Serum Proteins; Reduction in the Oxygen Saturation of the Arterial Blood, Ann. Int. Med. **9**:690, 1935. (*f*) Myers, W. K., and Keefer, C. S.: Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver, Arch. Int. Med. **55**:349 (March) 1935. (*g*) Tumen, H., and Bockus, H. L.: Clinical Significance of Serum Proteins in Hepatic Diseases Compared with Other Liver Function Tests, Am. J. M. Sc. **193**:788, 1937. (*h*) Foley, E. F.; Keeton, R. W.; Kendrick, A. B., and Darling, D.: Alterations of Serum Proteins as Index of Hepatic Failure, Arch. Int. Med. **60**:64 (July) 1937. (*i*) Butt, H. R.; Snell, A. M., and Keys, A.: Plasma Proteins in Hepatic Disease: A Study of the Colloid Osmotic Pressure of Blood Serum and of Ascitic Fluid in Various Diseases of the Liver, ibid. **63**:143 (Jan.) 1939. (*j*) Gray, S. J.: Colloidal Gold Reaction of Blood Serum in Diseases of the Liver, ibid. **65**:524 (March) 1940. (*k*) Ivanov, L. P., and Chervyakovskii, N. Y.: Changes in the Albumin Fraction in the Blood Serum in Liver Disease, abstracted, Chem. Abstr. **30**:6808, 1936. (*l*) O'Hare, J. P., and Driscoll, M.: Blood Proteins in Liver Disease, in Medical Papers Dedicated to Henry

(Footnote continued on next page)

ratio may be reversed in the presence of this disease. However, it has not been clear what relation the changes in serum protein bear to the course of the disease and to the formation of ascites.

Snell [2e] has stated that "the ratio tends to return to normal as improvement takes place," although he has not published data pertinent to this observation. Foley, Keeton, Kendrick and Darling [2h] reported data on 1 patient with cirrhosis of the liver and ascites whose ascites disappeared and whose clinical improvement was associated with a return of serum protein values to normal during a period of seven months. Conn, Newburgh, Johnston and Sheldon [3] recorded data on the serum proteins of a patient with hepatic disease, in whom improvement was associated with a rise in serum albumin to normal. This phenomenon occurred over a four month period when the patient had no ascites. O'Hare and Driscoll,[2l] and more recently Gray,[2j] have suggested that there may be a correlation between the extent of alteration of the albumin-globin ratio and the severity of hepatic disease, since patients with more advanced forms of disease of the liver seemed to have more extreme alterations of serum proteins. Tumen and Bockus,[2g] on the contrary, reported as follows:

> The ratio of the two proteins to each other fluctuated a great deal during the course of the disease without any striking change in the serum-albumin content, and without there being any apparent variation in the associated liver disturbance.

Likewise, several authors ascribed the formation of ascites in part to changes in the serum proteins. Peters and Eisenman,[2d] Myers and Keefer [2f] and Ivanov and Chervyakovskii [2k] found that the formation of ascites was closely related to a reduction in serum albumin. Butt, Snell and Keys [2i] stated that the colloid osmotic pressure of the serum was reduced in cirrhosis of the liver with ascites and that the lowered pressure was correlated roughly with a reduction in the level of serum albumin. They inferred that a low colloid osmotic pressure may play a part in the formation of ascites. Kellermann [4] found that the colloid osmotic pressure of the serum was reduced in patients with cirrhosis of the liver and ascites. The only comprehensive report of changes in serum protein during formation of ascites or during diuresis and the disappearance of ascites was that made by Foley and associates.[2h]

Asbury Christian, Baltimore, Waverly Press, Inc., 1936, p. 639. (*m*) Israel, H. L., and Reinhold, J. G.: Detection of Cirrhosis and Other Diseases of the Liver by Laboratory Tests, J. Lab. & Clin. Med. **23**:588, 1937.

3. Conn, J. W.; Newburgh, L. H.; Johnston, M. W., and Sheldon, J. W.: Study of the Deranged Carbohydrate Metabolism in Chronic Infectious Hepatitis, Arch. Int. Med. **62**:765 (Nov.) 1938.

4. Kellermann, J.: Das Verhalten des kolloidosmotischen (onkotischen) im Verlaufe von Lebererkrankungen, Ztschr. f. d. ges. exper. Med. **100**:377, 1937.

In the present study on patients with cirrhosis of the liver we have attempted to clarify the relationship between serum proteins and hepatic function by following changes in the protein fractions of serum, both during clinical improvement and during hepatic failure. Our results confirm the suggested correlation between the functional competence of the liver and changes in serum proteins. The trend of changes in the serum proteins, particularly in the serum albumin, is of prognostic significance. Furthermore, the formation of ascites seems to depend in part on the level of the serum albumin.

The data contained in this report represent part of the results of a four year study of patients with cirrhosis of the liver.[5] Serum proteins were determined at monthly intervals while the patients were in the hospital and every two months after their discharge.[6]

RELATION OF THE SERUM PROTEIN LEVEL TO THE CLINICAL COURSE

In figure 1 is charted the frequency distribution of values for serum albumin and for serum globulin determined for 61 patients at the time of their admission to the hospital. It is apparent that the general distribution falls beyond the normal range, a deviation which confirms reports by other workers.[7] The clinical states of the patients at the times these values were obtained varied considerably. Some patients had jaundice, ascites and edema. Others had only ascites or only jaundice. In still others the presenting problem was hematemesis. Thus the distribution of values is that of a heterogeneous group of patients, all, however, with cirrhosis of the liver.

Tables 1 through 6 record the changes in serum proteins occurring in these 61 patients throughout the period of study. Since the patients were seen in different stages of the disease and since there might well have been a correlation between the level of protein in the blood at the time of entry and the clinical outcome with respect to duration of life, the subjects were classified on the basis of prognosis. No patient was included if the course of his illness was terminated by a fatal episode unrelated to hepatic failure, such as primary carcinoma of the liver, carcinoma of the bile ducts, thrombosis of the portal vein, Pick's polyserositis or death following operation for an incarcerated umbilical hernia.

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5. Patek, A. J., Jr., and Post, J.: Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex, J. Clin. Investigation **20**:481, 1941.

6. The serum proteins were determined by the Howe method of precipitating the globulin fraction, together with the mico-Kjeldahl distillation technic.

7. Filinski.[1] Footnote 2 *a-k*.

The range of values for serum albumin, determined at the time of admission to the hospital, has been tabulated for a group of patients who improved and for a group of those who died. The 28 patients who made

Range of Values for Serum Albumin, Gm. per 100 Cc.	Number of Patients Who Died	Number of Patients Who Improved
1.5 - 2.5	14	7
2.5 - 3.5	6	15
3.5 - 4.5	0	5
4.5 - 5.0	0	1
Mean value and standard deviation, Gm. per 100 Cc.	2.4 ± 0.5	3.0 ± 0.7

clinical improvement were those included in tables 1 through 4. Improvement was measured by diuresis, with disappearance of ascites,

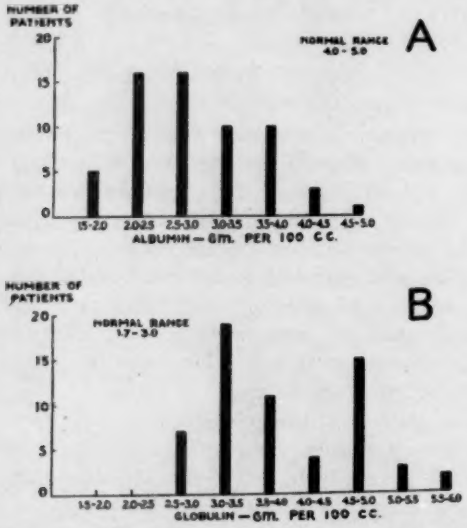

Fig. 1.—Frequency distribution of values for serum protein determined at the time of admission to the hospital for 61 patients with cirrhosis of the liver. *A*, values for serum albumin. *B*, values for serum globulin. In both instances the values fall wide of the normal range.

and by a return to previous strength and well-being. In certain patients (tables 1 and 2) these changes seemed nearly permanent. In others (tables 3 and 4) they were temporary or incomplete. Although some of the latter patients ultimately died of hepatic failure, the period of survival after admission to the hospital was never less than twelve months. In sharp contrast is the outcome of illness in the 20 patients (table 6) who failed to show any sustained improvement and whose course was generally characterized by progressive hepatic failure. The average survival period was three months.

The difference between the mean values for serum albumin for the two groups of patients is statistically significant. Therefore it appears that the level of the serum albumin has a prognostic value. Further examination of these data shows that all patients who died had ascites on admission to the hospital and that only 2 experienced a partial diuresis, which was temporary. These patients (44 and 49, table 6) had values for serum albumin of 2.9 and 3.3 Gm. per hundred cubic centimeters respectively on entry. However, 6 of the 28 patients who improved had no ascites. Their initial values for serum albumin ranged between 3.5 and 5.0 Gm. per hundred cubic centimeters.

When one compares only the values for patients who had ascites, the mean is 2.4 Gm. per hundred cubic centimeters (standard deviation $= \pm 0.5$ Gm.) for those who died and 2.7 Gm. (standard deviation $= \pm 0.5$ Gm.) for those who improved. The difference between the means is not statistically significant. Of the 20 patients who died, 70 per cent had serum albumin levels below 2.5 Gm. per hundred cubic centimeters. On the other hand, of the 22 patients who improved, 70 per cent had serum albumin levels above 2.5 Gm. Thus it appears that the prognosis as to duration of life becomes increasingly grave as the level of the serum albumin decreases.

The distribution of the serum globulin values for these same two groups of patients has been tabulated.

Range of Values for Serum Globulin, Gm. per 100 Cc.	Number of Patients Who Died	Number of Patients Who Improved
2.5 - 3.5	8	13
3.5 - 4.5	4	9
4.5 - 5.5	8	6
Mean value and standard deviation, Gm. per 100 Cc.	3.8 ± 0.8	3.8 ± 0.7

There is no difference between the mean values for serum globulin for these two groups. Thus the level of the serum globulin is of no prognóstic value.

The range of values for serum total protein of these groups of patients has also been tabulated.

Range of Values for Serum Total Protein, Gm. per 100 Cc.	Number of Patients Who Died	Number of Patients Who Improved
5.0 - 6.0	7	4
6.0 - 7.0	11	11
7.0 - 8.0	2	11
8.0 - 9.0	0	2
Mean, Gm. per 100 Cc.	6.3	6.6

These data show a possibly higher range distribution for those patients who improved. However, since the normal range of values for the serum total protein is between 6.0 and 8.0 Gm. per hundred cubic centimeters, any variation from patient to patient within this range is meaningless.

TABLE 1.—*Changes in Values for Serum Proteins in*

No.	Period of Observation		Month 0	1	2	3	4	5	6	7	8	9	10	11	12
1	3/29/39 to 6/29/39	Albumin	**3.3** †	**4.1**	**4.3**	...	...	...	...	...	...	...	...	...	...
		Globulin	**3.2**	**3.5**	**3.4**	...	...	...	...	...	...	...	...	...	...
2	4/28/36 to 9/25/36	Albumin	**3.3** †	**4.1**	**4.2**	**4.4**	**4.3**	**4.7**	...	...	...	...	...	...	...
		Globulin	**3.8**	**4.4**	**4.3**	**3.8**	**3.6**	**3.7**	...	...	...	...	...	...	...
3	7/ 1/39 to 4/ 2/40	Albumin	**2.4** †	**3.0**	**3.5**	**4.2**	**4.1**	**3.9**	**3.9**	**3.8**	**4.4**	**3.9**	**4.2**	...	...
		Globulin	**3.5**	**3.9**	**3.1**	**2.8**	**2.6**	**2.9**	**2.8**	**1.9**	**2.9**	**2.7**	**2.8**	...	...
4	8/ 6/37 to 1/16/38	Albumin	**1.8**	**2.6** †	**3.4**	**3.9**	**4.0**	...	**3.2**	...	...	...	...	...	...
		Globulin	**3.5**	**4.5**	**4.2**	**3.6**	**3.7**	...	**3.6**	...	...	...	...	...	...
5	3/21/39 to 9/11/39	Albumin	**3.5**	**2.1**	**2.1**	**2.4**	**2.8** †	**3.0**	**3.2**	...	...	**4.0**	...	...	...
		Globulin	**3.1**	**3.9**	**3.9**	**4.0**	**3.9**	**3.8**	**3.6**	...	...	**3.5**	...	...	...
6	4/ 2/37 to 10/ 6/37	Albumin	**2.2** †	**2.5**	**2.8** †	**3.0**	**3.2**	**3.2**	**3.5**	...	...	...	**3.4**	...	...
		Globulin	**3.5**	**3.3**	**2.9**	**3.5**	**3.4**	**3.2**	**3.2**	...	...	...	**3.7**	...	...
7	1/28/38 to 6/ 5/39	Albumin	**2.7**	**3.1** †	**3.6**	**3.8**	...	**3.8**	...	...	**3.4**	**3.4**	...	**3.5**	**3.7**
		Globulin	**4.7**	**4.1**	**4.5**	**3.0**	...	**3.5**	...	...	**3.1**	**3.3**	...	**3.3**	**2.8**
8	12/20/37 to 5/ 4/39	Albumin	†**3.0**	**4.1**	**4.8**	**3.9**	**4.6**	**4.6**	**5.4**	...	**5.0**	**4.6**	**4.8**	**4.9**	**4.8**
		Globulin	**3.6**	**4.2**	**3.7**	**2.3**	**2.8**	**2.7**	**2.4**	...	**2.9**	**2.5**	**2.4**	**2.7**	**2.1**
9	5/ 9/38 to 3/ 1/40	Albumin	**3.2**	**2.8**	**3.2**	**3.1**	**3.3**	**2.8** †	**3.1**	**3.3**	**3.5**	**3.4**	**3.7**	**3.4**	**4.1**
		Globulin	**2.9**	**3.1**	**3.2**	**3.2**	**3.7**	**4.3**	**4.5**	**4.4**	**4.2**	**4.3**	**4.2**	**3.8**	**4.3**
10	1/ 7/38 to 11/25/39	Albumin	**3.3**	**3.4**	**3.1**	**3.5**	**2.9**	**3.0**	**2.9**	... †	**3.3**	**3.6**	**3.9**	**3.9**	**4.1**
		Globulin	**3.5**	**3.7**	**3.5**	**2.3**	**2.1**	**2.2**	**2.1**	...	**2.5**	**2.8**	**2.6**	**2.8**	**2.7**
11	10/ 5/36 to 1/18/38	Albumin	**2.2**	**2.6** †	**3.4**	**3.4**	**3.6**	**3.5**	**3.7**	**3.9**	...	**3.9**	...	**4.3**	**4.4**
		Globulin	**2.8**	**2.6**	**2.9**	**3.3**	**3.2**	**3.0**	**3.0**	**3.4**	...	**3.1**	...	**3.1**	**3.8**
12	9/22/36 to 6/ 1/40	Albumin	**2.3**	...	**3.3** †	**3.8**	**4.1**	**4.1**	**4.3**	**3.9**	**4.5**	**4.5**	...	**4.0**	**4.2**
		Globulin	**3.6**	...	**2.3**	**4.0**	**4.0**	**3.3**	**3.5**	**3.5**	**3.9**	**3.9**	...	**3.9**	**3.1**

			Weeks 0	1	2	6	8	8½	10	14	18	22	30	34	38
13	1/14/38 to 5/ 8/39	Albumin	**2.8**	**3.1** †	**3.1**	**3.0**	**2.5**	**2.5**	**2.1** †	**3.2**	**2.4**	**3.5**	**3.7**	**3.7**	**3.8**
		Globulin	**4.5**	**4.9**	**4.5**	**4.7**	**4.5**	**4.2**	**3.2**	**4.2**	**3.9**	**3.3**	**3.4**	**3.2**	**3.0**

* Heavy type indicates the presence of ascites, and light type indicates the absence of ascites.
† Approximate time of onset of diuresis.

TABLE 2.—*Changes in Values for Serum Proteins in*

No.	Period of Observation		Month 0	1	2	3	4	5	6	7	8	9	10	11	12
14	1/26/37 to 10/ 9/37	Albumin	**3.7**	**3.8**	**4.2**	**4.2**	**3.7**	**3.9**	**3.9**	**4.2**	**3.9**	...	...	...	...
		Globulin	**3.9**	**3.6**	**3.0**	**2.9**	**3.3**	**3.0**	**3.1**	**3.1**	**2.7**	...	...	...	...
15	11/27/36 to 4/ 1/37	Albumin	**4.2**	**4.2**	**4.2**	**4.3**	**4.4**	...	...	...	...	...	...	...	...
		Globulin	**4.5**	**3.8**	**3.8**	**3.5**	**3.2**	...	...	...	...	...	...	...	...
17	11/ 1/38 to 3/16/40	Albumin	**3.6**	**4.0**	**4.5**	**4.8**	**4.6**	**4.9**	**4.6**	**4.9**	**4.5**	**4.6**	...	**4.7**	**4.4**
		Globulin	**3.6**	**3.1**	**3.5**	**3.4**	**3.4**	**2.7**	**3.1**	**3.1**	**3.3**	**3.3**	...	**2.9**	**3.6**
18	10/19/39 to 4/25/40	Albumin	**4.3**	**3.7**	...	...	...	...	...	**4.5**	**4.4**	**4.0**	**5.2**	**5.1**	...
		Globulin	**3.3**	**3.2**	...	...	...	...	...	**3.3**	**3.1**	**2.9**	**2.7**	**2.7**	...
16	3/13/37 to 12/23/37	Albumin	**3.7**	**3.3**	**3.9**	...	**4.1**	**3.8**	**4.1**	**3.9**	...	**3.9**	**4.9**	...	...
		Globulin	**3.1**	**2.0**	**2.4**	...	**3.0**	**2.5**	**3.0**	**3.0**	...	**2.5**	**2.8**	...	...
19	12/28/37 to 2/11/39	Albumin	**3.9**	**4.1**	**4.3**	**4.4**	**4.2**	**4.6**	...	...	**4.3**	**4.0**	**4.4**	**4.6**	**4.5**
		Globulin	**4.7**	**4.6**	**4.3**	**3.0**	**2.8**	**3.0**	...	...	**3.6**	**3.4**	**3.2**	**2.7**	**2.6**
20	4/28/37 to 9/ 1/39	Albumin	**3.8**	**4.5**	**4.3**	**4.4**	**4.6**	**4.4**	...	**4.8**	...	**4.8**	...	**5.0**	**4.9**
		Globulin	**2.7**	**2.9**	**2.3**	**2.9**	**2.7**	**2.5**	...	**2.5**	...	**2.5**	...	**3.3**	**3.4**

*Patients with Ascites Who Made Clinical Improvement**

Month												
13	14	15	16	18	20	22	26	30	36	40	45	Comment
...	...	...	...	...	...	...	...	...	...	...	...	Gastrointestinal hemorrhage in seventh month of observation
...	...	...	...	...	...	...	...	...	...	...	...	Massive fatal gastrointestinal hemorrhage in sixth month of observation; diagnosis at necropsy: cirrhosis of liver and ruptured esophageal varix
...	...	...	...	...	...	...	...	...	...	...	...	Evidence of recent gastrointestinal hemorrhage when observation was begun; dehydration
...	...	...	...	...	...	...	...	...	...	...	...	Admission to hospital 2/13/38; death 2/15/38; diagnosis at necropsy: uremia, chronic pyelonephritis, arteriosclerosis and cirrhosis of liver
3.8	3.9	4.0	3.8	3.8	...	4.3	4.4					
3.0	3.0	3.1	3.0	3.2	...	3.5	2.8					
4.3	4.9	5.0	...	...	...	...	...	...	...	...	...	Death 5/4/39; diagnosis at necropsy: cerebrovascular syphilis with thrombosis, bronchopneumonia and cirrhosis of liver
2.3	2.9	2.3										
4.3	4.2	4.0	4.0	3.8	...	4.5						
4.0	3.9	3.9	3.7	3.8	...	3.5						
3.5	4.1	3.8	...	3.9	4.6	...	...	4.7	...	...	...	Operation for strangulated umbilical hernia in thirteenth month of observation
2.6	3.0	3.1	...	3.1	3.3	...	...	2.7				
...	4.4	4.3	4.0	4.4	...	4.1	4.4	4.4	4.5	4.9		
...	4.2	3.2	2.8	3.3	...	2.9	2.9	3.1	2.6	3.1		
...	4.5	4.7	4.7	...	5.2	...	4.3	4.7	4.4	4.5	4.5	
...	2.7	2.6	2.6	...	2.8	...	3.3	3.2	3.0	2.5	2.7	

Weeks								
42	46	50	54	60	62	69	75	85	
3.9	3.8	3.7	3.9	3.8	3.8	3.9	4.3	4.5	Acute glomerulonephritis in eighth week of observation; infection of the upper respiratory tract with jaundice and edema lasting 1 week during sixtieth week of observation
3.3	3.0	2.7	3.4	3.3 †	3.6	3.2	3.3	3.3	

The question mark indicates that the presence of ascites was not excluded.

Patients Without Ascites Who Made Clinical Improvement

Month											
13	14	15	16	18	19	22	25	28	31	32	Comment
...	...	...	...	...	...	...	...	...	...	...	Severe jaundice; malnutrition
...	...	...	...	...	...	...	...	...	...	...	Malnutrition; peripheral neuritis
...	...	...	...	...	...	...	...	...	...	...	Jaundice; peripheral neuritis
...	...	...	...	...	...	...	...	...	...	...	Peripheral neuritis
...	4.8	...	...	...	...	...	...	4.9	...	...	Severe jaundice; peripheral neuritis
...	3.5	...	...	...	...	...	...	2.6			
...	...	...	5.0	5.2	5.3	...	...	...	...	...	Malnutrition; peripheral neuritis
...	...	...	3.4	3.4	2.4						
4.6	5.3	5.6	...	5.1	4.9	...	4.9	5.6	4.9	5.5	Malnutrition; peripheral neuritis
2.7	2.0	1.9	...	2.5	2.3	...	2.7	2.2	3.1	2.4	

Apparently the levels of total protein and of globulin in the serum are without prognostic import in cases of cirrhosis of the liver. However, there is some correlation between the level of serum albumin and the prognosis as to duration of life.

The progressive changes in serum proteins during the course of cirrhosis of the liver were then examined. In table 1 are listed data for 13 patients who had ascites on admission and who subsequently

TABLE 3.—*Changes in Values for Serum Proteins for*

No.	Period of Observation		Month 0	1	2	3	4	5	6	7	8	9	10	11	12
22	7/7/38 to 3/10/40	Albumin	2.8	3.4	3.6	3.5	3.8	3.5	2.9	3.3	3.7	...	...	...	2.8
		Globulin	3.2‡	3.4 †	3.2	2.7	3.0	2.8	2.5‡	4.1 †	3.4	...	...	...	2.8‡

* Heavy type indicates the presence of ascites, and light type indicates the absence of ascites.
† Approximate time of onset of diuresis.
‡ Gastrointestinal hemorrhage.

TABLE 4.—*Changes in the Values for Serum Proteins for*

No.	Period of Observation		Month 0	1	2	3	4	5	6	7	8	9	10	11	12
23	1/ 7/38 to 8/16/39	Albumin	2.4	2.6 †	2.6	2.5	2.8	2.5	2.4	...	2.8	2.7	2.9	3.0	2.9
		Globulin	4.8	5.2	4.3	3.9	3.4	3.4	3.5	...	3.3	3.1	3.3	3.5	3.1
24	12/29/37 to 4/25/40	Albumin	3.2	2.9	3.3	3.1 †	3.1	3.5	3.4	...	...	3.7	3.3	3.1	3.1
		Globulin	3.3	3.9	3.3	3.3	3.5	3.5	3.3	...	...	3.6	3.4	3.5	3.5
27	11/ 5/38 to 3/18/39	Albumin	2.9	3.1 †	3.6	3.1	3.4	...	...	3.7	...	...	...	...	...
		Globulin	4.5	4.8	4.2	4.4	4.1	...	...	4.6	...	...	...	...	...
28	5/24/39 to 5/24/40	Albumin	2.9	2.8	2.7 †	2.9	3.4	3.4	3.3	3.3	2.8	3.5	3.6	3.4	3.2
		Globulin	5.7	4.9	4.6	4.0	4.1	3.9	5.1	4.9	4.8	4.0	3.9	4.0	3.9
29	1/12/39 to 11/ 1/40	Albumin	2.7	2.4 †	2.7	3.5	3.1	2.7	2.7	3.2	3.0	3.1	3.4	3.3	3.2
		Globulin	3.3	3.1	3.5	3.0	3.4	2.9	2.6	2.7	3.0	3.1	3.1	3.1	3.1
25	12/20/37 to 3/ 5/40	Albumin	2.5 †	3.0	3.1	3.2	3.3	3.4	3.3	3.1	...	3.0	3.0	3.2	2.9
		Globulin	3.4	5.1	5.1	5.1	4.1	3.9	3.8	3.5	...	4.4	4.4	4.3	4.2
26	9/16/37 to 1/23/40	Albumin	1.8	2.0	2.2	2.1	1.9	2.0	2.3	2.2	2.2	2.6	2.4	...	2.7
		Globulin	5.3	5.0	4.7	4.4	5.3	5.6	5.7	5.1	4.4	4.6	3.8	...	5.0

* Heavy type indicates the presence of ascites, and light type indicates the absence of ascites.
† Approximate time of onset of diuresis.
? Question mark indicates that the presence of ascites was not excluded.

improved. All of them showed the classic signs of decompensated cirrhosis of the liver. On admission their values for serum albumin ranged from 1.8 to 3.5 Gm. per hundred cubic centimeters. It is apparent that a sustained rise in the amount of serum albumin attended clinical improvement and diuresis. In all patients but 1 (patient 6) the serum albumin rose to normal. In some instances the value for serum globulin returned to normal, whereas in others it remained somewhat elevated. It is of further interest that the changes in serum proteins in these patients generally occurred over many weeks.

The albumin and globulin values for 7 patients who were less severely ill are recorded in table 2. None of the patients had ascites; nevertheless, all of them revealed ample evidence of cirrhosis of the liver. Patients 14 and 16 were extremely jaundiced. All but patient 14 showed severe peripheral neuritis. Although the deviations from normal were less pronounced than those recorded in table 1, there was a definite tendency toward reduced values for albumin and increased values for

*Patient 22, Who Had Repeated Gastrointestinal Hemorrhages**

Month							Comment
13	14	15	16	17	18	19	
3.1	3.2	3.6	...	3.6	3.9	3.7	Death 3/10/40; diagnosis at necropsy: cirrhosis of liver, ruptured esophageal varix and thrombosis of portal vein
3.1 †	3.0	3.2	...	3.1	3.2	3.3?	

*Patients with Ascites Who Made Partial Clinical Improvement**

Month																Comment
13	14	15	16	18	19	20	21	22	23	24	25	26	27	28	29	
3.1	3.2	3.3	2.9	2.9	2.8	3.4	...	...	...	...	...	...	...	...	...	Death November 1939; no necropsy
3.1	3.3	3.2	2.8	2.9	3.2	3.5	...	...	...	...	...	...	...	...	...	
3.3?	3.2?	3.5?	3.6?	3.4	3.7	3.6	3.1	3.1	3.2	3.4	3.5	3.6	2.8	...	...	Suspected thrombosis of splenic and portal veins; death 4/25/40; no necropsy
3.0	3.3	3.6	3.4	3.2	3.0	3.4	3.7	3.4	3.4	3.6	3.3	3.1	3.5			
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Patient last observed in June 1939; no ascites; general health poor
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Patient still under observation
3.3	3.5	3.1	3.1	3.0	3.0	...	2.7	...	...	...	...	...	...	...	...	Patient still under observation
2.9	2.9	2.8	2.8	3.0	2.8	...	2.9									
3.1	3.3	3.1	3.3	3.5	3.5	3.5	3.3	3.3	...	3.2	3.1	2.4	...	...	...	Death 3/5/40; diagnosis at necropsy: cirrhosis of liver
3.8	3.5	3.1	3.0	3.4	3.4	3.9	3.9	4.0	...	3.5	3.6	3.4				
2.9†	3.6	2.7	2.8	2.6	2.7	3.0	3.2	3.0	...	2.9	...	2.9	2.6	2.8	2.2	Death 1/23/40; diagnosis at necropsy; carcinoma of liver with primary metastasis to portal vein, lungs and adrenals and cirrhosis of liver
4.8	4.8	4.8	5.0	4.5	5.2	4.8	4.8	4.5	...	4.5	...	4.7	5.2	4.8	4.8	

globulin at the time of admission. The initial value for albumin ranged from 3.6 to 4.3 Gm. per hundred cubic centimeters. Improvement in the general clinical state was accompanied by a change toward normal values both for albumin and for globulin.

In contrast to the foregoing data are those for the 7 patients included in table 4. The clinical condition of the latter patients appeared to be similar to that of the patients listed in table 1, both during the state of decompensation and during temporary improvement. The level of serum albumin on entry ranged from 1.8 to 3.2 Gm. per hundred cubic

TABLE 5.—*Changes in Values for Serum Proteins in Patients Whose Hepatic Disease Was Complicated or Who Were Incompletely Studied* *

No.	Period of Observation		Month 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Comment
30	10/14/38 to 11/10/38	Albumin	3.7	3.8	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Death 11/26/38; diagnosis at necropsy: primary carcinoma of liver, cirrhosis of liver and generalized arteriosclerosis
		Globulin	2.6	2.6															
31	2/23/38 to 4/21/38	Albumin	2.6	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Death 4/21/38, after operation for strangulated, incarcerated umbilical hernia; cirrhosis of liver diagnosed after biopsy
		Globulin	5.8																
32	2/25/38 to 3/ 6/38	Albumin	2.3	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Patient signed out at own request
		Globulin	5.0																
33	11/20/36 to 1/ 7/37	Albumin	2.7	2.9	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Death 1/7/37; diagnosis at necropsy: primary carcinoma of liver, cirrhosis of liver and intraperitoneal hemorrhage
		Globulin	3.4	3.7															
34	1/ 6/38 to 1/15/38	Albumin	2.5	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Patient discharged 1/15/38 to Psychiatric Division of Bellevue Hospital; death January 1938; no necropsy; diabetes mellitus
		Globulin	4.5																
35	8/18/37 to 8/20/37	Albumin	2.2	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Death 8/20/37; diagnosis at necropsy: primary carcinoma of liver and cirrhosis of liver
		Globulin	3.1																
36	8/18/37 to 9/24/37	Albumin	3.5	3.3	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Patient signed out at own request
		Globulin	4.4	4.4															
37	3/23/38 to 1/16/39	Albumin	3.6	3.4	3.1	3.5	3.2	...	3.4	2.8	3.1	3.5	3.6	...	...	...	...	...	Death 1/16/39; diagnosis at necropsy: cirrhosis of liver, thrombosis of portal vein and infarcts of liver due to thromboses
		Globulin	4.3	3.2	3.5	3.1	3.1	...	2.8	3.2	3.3	2.7	3.3						
38	10/22/37 to 12/20/38	Albumin	2.9	2.6	2.7	2.7	2.9 †	3.5	2.7	2.9	2.7	2.8	...	3.0	2.7	2.7	2.7	2.0	Death 12/20/38; diagnosis at necropsy: cirrhosis of liver, Pick's polyserositis and intraperitoneal hemorrhage
		Globulin	3.4	3.3	3.9	5.9	6.1	5.0	4.3	3.2	3.1	3.1	...	3.6	3.3	3.6	3.3	2.3	
39	2/25/38 to 11/ 7/38	Albumin	2.7	...	...	...	...	...	3.2	...	...	3.1	...	...	...	...	...	...	Observed at irregular intervals
		Globulin	2.9	...	...	...	...	...	3.0	...	...	3.2							
40	5/22/39 to 2/17/40	Albumin	2.4	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Patient followed incompletely; discharged 2/17/40 to Psychiatric Division of Bellevue Hospital; diagnosis: cerebral arteriosclerosis
		Globulin	4.7																
41	11/ 6/37 to 4/ 3/38	Albumin	4.4	4.4	3.6	3.9	3.2	...	...	...	...	...	...	...	...	...	...	...	Death 4/3/38; diagnosis at necropsy: primary carcinoma of bile ducts with metastasis to porta hepatis, biliary cirrhosis of liver and recanalization of thrombosed intrahepatic portal veins
		Globulin	1.9	2.2	3.0	2.3	2.3												
21	8/14/39 to 11/22/39	Albumin	4.4	...	...	4.5	...	...	...	...	...	...	...	...	...	...	...	...	Cirrhosis of liver diagnosed after biopsy; patient observed at irregular intervals
		Globulin	2.5	...	...	2.6													

* Heavy type indicates the presence of ascites, and light type indicates the absence of ascites.
† Approximate time of onset of diuresis.

TABLE 6.—*Changes in Values for Serum Proteins in Patients Who Died of Cirrhosis of the Liver* *

No.	Period of Observation		Month 0	1	2	3	4	5	6	7	8	9	10	11	Comment
43	9/16/37 to 10/11/37	Albumin	**2.4**	...	...	...	...	...	...	...	...	...	...	...	Death 10/11/37; diagnosis at necropsy: cirrhosis of liver, pneumococcic pericarditis and bronchopneumonia
		Globulin	**2.7**												
58	1/ 3/39 to 1/24/39	Albumin	**2.7**	...	...	...	...	...	...	...	...	...	...	...	Death 1/24/39; diagnosis at necropsy: cirrhosis of liver and ruptured esophageal varix
		Globulin	**4.1**			-									
59	12/ 5/39 to 1/ 5/40	Albumin	**2.8**	...	...	...	...	...	...	...	...	...	...	...	Death 1/5/40; no necropsy
		Globulin	**3.9**												
61	7/ 7/38 to 8/ 9/38	Albumin	**1.9**	**2.0**	...	...	...	...	...	...	...	...	...	...	Death 8/9/38; diagnosis at necropsy: cirrhosis of liver
		Globulin	**4.9**	**4.4**											
42	9/22/36 to 10/18/36	Albumin	**2.3**	**1.7**	...	...	...	...	...	...	...	...	...	...	Death 10/18/36; diagnosis at necropsy: cirrhosis of liver
		Globulin	**2.6**	**3.5**											
45	9/17/38 to 10/18/38	Albumin	**2.3**	**2.3**	...	...	...	...	...	...	...	...	...	...	Death 10/18/38: diagnosis at necropsy: cirrhosis of liver and acute diffuse peritonitis
		Globulin	**3.2**	**2.9**											
46	7/12/38 to 9/13/38	Albumin	**2.1**	**2.4**	...	...	...	...	...	...	...	...	...	...	Death 9/13/38; no necropsy
		Globulin	**4.6**	**3.8**											
47	10/14/37 to 11/19/37	Albumin	**2.2**	**1.9**	...	...	...	...	...	...	...	...	...	...	Death 11/19/37; diagnosis at necropsy: cirrhosis of liver
		Globulin	**4.5**	**4.6**											
48	11/ 3/37 to 12/11/37	Albumin	**2.0**	**2.0**	...	...	...	...	...	...	...	...	...	...	Death at home, February 1938; no necropsy
		Golbulin	**3.1**	**3.6**											
51	6/ 4/37 to 6/29/37	Albumin	**1.5**	**1.4**	...	...	...	...	...	...	...	...	...	...	Death 6/29/37; diagnosis at necropsy: cirrhosis of liver
		Globulin	**4.7**	**4.8**											
53	8/25/37 to 9/21/37	Albumin	**1.8**	**1.8**	...	...	...	...	...	...	...	...	...	...	Death 9/21/37; no necropsy
		Globulin	**3.9**	**3.4**											
56	7/18/39 to 9/12/39	Albumin	**1.9**	**1.8**	...	...	...	...	...	...	...	...	...	...	Death 9/12/39; no necropsy
		Globulin	**3.6**	**3.6**											
57	1/20/37 to 2/16/37	Albumin	**3.0**	**2.6**	...	...	...	...	...	...	...	...	...	...	Death 2/15/37; diagnosis at necropsy: cirrhosis of liver
		Globulin	**4.5**	**5.3**											
60	4/ 3/40 to 5/23/40	Albumin	**2.1**	...	...	...	...	...	...	...	...	...	...	...	Death 5/23/40; no necropsy
		Globulin	**4.5**												
50	9/28/37 to 12/ 2/37	Albumin	**2.3**	**1.8**	**1.8**	...	...	...	...	...	...	...	...	...	Death 12/2/37; diagnosis at necropsy: cirrhosis of liver, thrombosis of portal vein and duodenal ulcer
		Globulin	**4.8**	**4.5**	**5.2**										
52	4/ 3/37 to 6/14/37	Albumin	**2.2**	**2.4**	**2.9**	...	...	...	...	...	...	...	...	...	Death 6/14/37; diagnosis at necropsy: cirrhosis of liver
		Globulin	**3.2**	**2.9**	**3.3**										
55	8/28/39 to 1/ 9/40	Albumin	**2.1**	**2.2**	**2.2**	**2.0**	**2.0**	...	...	...	...	...	...	...	Death 1/9/40; diagnosis at necropsy: cirrhosis of liver
		Globulin	**4.5**	**5.2**	**4.9**	**4.7**	**4.8**								
44	12/ 8/37 to 3/24/38	Albumin	**2.9** †	**3.7**	3.3	3.3	...	...	...	...	...	...	...	...	Death 3/24/38; diagnosis at necropsy: cirrhosis of liver and ruptured esophageal varix
		Globulin	**2.7**	4.0	3.4	2.1									
54	2/16/39 to 8/ 5/39	Albumin	**3.0**	**2.7**	**2.8**	**3.3**	**2.8**	**2.8**	**2.7**	**2.6**	**2.3**	...	...	...	Death 8/5/39; diagnosis at necropsy: cirrhosis of liver and duodenal ulcer
		Globulin	**3.3**	**3.2**	**2.7**	**2.1**	**2.5**	**2.6**	**2.2**	**1.6**	**1.9**				
49	10/28/37 to 9/30/38	Albumin	**3.3** †	**3.4**	3.4	3.7	3.4	3.1	3.4	3.3	**3.0**	...	**2.6**	**2.7**	Death at home, December 1938; no necropsy; intraperitoneal hemorrhage (?)
		Globulin	**2.8**	**3.0**	3.0	4.3	4.3	3.5	3.4	3.2	**3.7**	...	**4.0**	**3.9**	

* Heavy type indicates the presence of ascites, and light type indicates the absence of ascites.
† Approximate time of onset of diuresis.

centimeters. Each of the 7 patients experienced at least one period of diuresis and a concomitant rise in the level of the serum albumin. However, in no case did the level of serum albumin remain normal over long periods of observation, in spite of clinical well-being during part of the time.

The course of patient 25 (table 4) is worthy of mention. This 54 year old man was admitted with massive ascites, edema and jaundice. The albumin-globulin ratio was 2.5 : 3.4. During the first six weeks of his stay in the hospital complete diuresis occurred and the jaundice disappeared. After this improvement he gained 20 pounds (9.1 Kg.). He was free of ascites and in good general health for two years. However, the level of serum albumin never became normal; it varied between 3.1 and 3.5 Gm. per hundred cubic centimeters, while values for serum globulin ranged between 2.9 and 5.1 Gm. Because of the persistently abnormal blood protein pattern the patient was considered to have poor "liver reserve." In spite of this, he left the hospital apparently in good health, only to return in three weeks with massive edema and ascites. The level of serum albumin had fallen to 2.4 Gm. per hundred cubic centimeters and that of serum globulin to 3.4 Gm. He died after three days. At autopsy the diagnosis of cirrhosis of the liver was confirmed.

Patients 23 and 24 (table 4) died, but no autopsy was performed in either instance. The condition of patient 26 was complicated by the presence of a primary carcinoma of the liver. We have been unable to follow patient 27. When last seen she had jaundice, but no ascites, and appeared to be in poor health. Patient 29 left the hospital in June 1940 in good condition. His serum albumin did not change significantly during the succeeding months, until September 7, when it was 2.6 Gm. per hundred cubic centimeters. On September 21 he was seen again, and at this time he was in poor general condition, with massive ascites and moderate edema of the legs. The value for serum albumin was 2.7 Gm. per hundred cubic centimeters and that for globulin 2.9 Gm. Patient 28 is still under observation. This patient has had complete diuresis, with marked clinical improvement. However, over a period of eight months the level of serum albumin has failed to become normal, and for this reason the patient is included in this group.

The course of these 7 patients is in sharp contrast to that of the patients whose values for blood protein are recorded in tables 1 and 2. Some of the latter have been followed for as long as three and one-half years after discharge from the hospital. During this time they have remained in good health. Thus, when clinical improvement is not associated with a sustained rise of serum albumin to normal, or nearly normal, the prognosis as to duration of life must be guarded.

In table 6 are recorded data on 20 patients whose clinical course was characterized by progressive hepatic failure. The course of illness was usually short, averaging three months. In no instance was a sustained rise in serum albumin noted.

RELATION OF THE SERUM PROTEIN LEVEL TO THE FORMATION OF ASCITES

Since Starling's [8] original work on the role of the serum proteins in the maintenance of the osmotic pressure of the blood, numerous investigators have stressed the important relation between alterations in the blood proteins and the formation of edema. According to Loeb

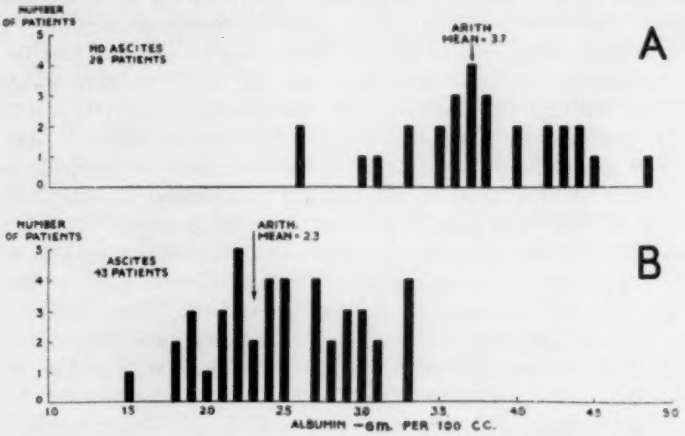

Fig. 2.—Frequency distribution of values for serum protein for patients with and without ascites. *A*, values for serum albumin for 28 patients with cirrhosis of the liver but no ascites. *B*, values for serum albumin for 43 patients with cirrhosis of the liver and ascites. The respective arithmetic mean values are indicated above each graph. Although there is some overlapping in each group, the means are significantly different from each other.

and associates,[9] ascitic fluid may also be considered a transudate. Consequently, a comparison was made of the values for serum proteins for patients with and without ascites. Figure 2 shows the frequency distribution of the values for serum albumin for 43 patients with ascites and 28 patients without ascites. The values recorded for the 43 patients with

8. Starling, E. H.: On the Absorption of Fluids from the Connective Tissue Spaces, J. Physiol. **19**:312, 1895.

9. Loeb, R. F.; Atchley, D. W., and Palmer, W. W.: On the Equilibrium Condition Between Blood Serum and Serous Cavity Fluids, J. Gen. Physiol. **4**: 591, 1922.

ascites represent those obtained at the time of admission to the hospital. Fifteen patients subsequently experienced complete diuresis and were included, with 13 others, among those without ascites. The values for albumin used for these 15 patients were those determined two months after diuresis was considered complete, in order to be certain of the absence of ascites.

The distribution of values for serum albumin is strikingly different in these two groups. The values for serum albumin for patients with ascites range between 1.5 and 3.3 Gm. per hundred cubic centimeters, whereas those for patients without ascites range between 2.6 and 4.8 Gm. The mean value for the group with ascites is 2.3 Gm. (standard deviation = ± 0.1), whereas that of the group without ascites is 3.7 Gm. (standard deviation = ± 0.8). The means are significantly different. The 2 patients whose level of serum albumin was 2.6 Gm. per hundred cubic centimeters in the absence of ascites had serum globulin values of 5.8 and 4.3 Gm. per hundred cubic centimeters, respectively. It is possible that in these 2 instances the globulin fractions played a significant role as osmotically active colloids. However, we have seen patients with ascites who had albumin and globulin values identical with these. The role of the serum globulin is obscure in this respect. When the mean values for total protein were examined, they were found to be 6.3 Gm. per hundred cubic centimeters for patients with ascites and 7.3 Gm. for those without ascites. For patients with ascites the mean value for serum globulin was 3.9 Gm. per hundred cubic centimeters, and for those without ascites it was 3.7 Gm. These mean values for total protein and for globulin are not significantly different in the two groups of patients.

Our data concerning the occurrence of low levels of serum albumin in patients with cirrhosis of the liver and ascites are similar to those already presented by other authors.[10] We have examined the data of Tumen and Bockus.[2g] Of 13 patients with cirrhosis of the liver and ascites, only 1 had a level of serum albumin above 3.5 Gm. per hundred cubic centimeters. Analysis of similar data reported by Foley and coworkers [2h] shows that in 21 cases of cirrhosis of the liver with associated ascites values for serum albumin range between 1.3 and 3.1 Gm. per hundred cubic centimeters. The range of values for serum globulin was 2.3 to 5.7 Gm. Abrami and Wallich [2b] recorded data for 15 patients with cirrhosis of the liver and associated ascites; the values for serum albumin ranged from 1.4 to 3.1 Gm. per hundred cubic centimeters and those for serum globulin from 2.8 to 5.3 Gm. In 2 instances of alcoholism with hepatomegaly, but without ascites, the values for the serum albumin and the serum globulin were each 4 Gm. per hundred cubic

10. Footnote 2 *b*, *d*, *g*, *h*, *i* and *l*.

centimeters. Thus it appears that ascites rarely occurs when the level of serum albumin is greater than 3.5 Gm. per hundred cubic centimeters. As suggested by other workers,[11] such a reduction in the serum albumin would lead to decreased osmotic pressure in the blood, which, in turn, would favor the accumulation of ascitic fluid.

It is not implied that reduction of the serum albumin is the only cause for the formation of ascites. It is likely that hypertension of the portal vein plays a contributory part. By direct measurement Thompson, Caughey, Whipple and Rousselot [12] showed that hypertension of the splenic vein occurs in patients with Banti's syndrome. In cases of Laennec's cirrhosis, also, there is ample clinical evidence of increased pressure in the portal system. MacIndoe's [13] perfusion studies, performed on human subjects post mortem, showed increased resistance in the cirrhotic liver when liquid material was perfused through the portal vein.

It seems unlikely that anatomic changes in the liver sufficient to alter the degree of portal pressure could take place within a few days or weeks and could thus promote diuresis, with the loss of ascites. Moreover, the degree of fibrosis in the liver (and presumably of portal hypertension) must vary considerably from patient to patient. If portal hypertension were the sole cause of ascites, there would be no such correlation between the presence of ascites and the level of the serum albumin as was observed. Data for patient 22 indicate that despite clinical and anatomic evidence of severe portal hypertension ascites occurred only after hemorrhage, associated with a loss of blood protein, as well as a loss of blood cells. Diuresis occurred when the level of serum albumin rose.

For these reasons, admittedly speculative, the level of the serum albumin appears to be an essential factor in the formation of ascites. It also seems likely that portal hypertension determines the site at which the transfer of fluid takes place.

RELATION OF THE SERUM PROTEIN LEVEL TO DIURESIS

Nineteen instances of diuresis in 17 patients are recorded in tables 1, 3 and 4, as follows: table 1, patients 1 through 11 and patient 13; table 3, patient 22, and table 4, patients 23, 25, 27 and 28. In each instance the diuresis was proved by a decrease in abdominal fluid and

11. Butt, Snell and Keys.[21] Ivanov and Chervyakovskii.[2k] Kellermann.[4]

12. Thompson, W. P.; Caughey, J. L.; Whipple, A. O., and Rousselot, L. M.: Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome), J. Clin. Investigation **16**:571, 1937.

13. MacIndoe, A. H.: Vascular Lesions of Portal Cirrhosis, Arch. Path. **5**: 23 (Jan.) 1928.

by a negative water balance. It is difficult to fix the exact time at which the onset of diuresis occurs, because this phenomenon may persist for several weeks. On this account the temporal relationship of diuresis and the level of serum albumin can only be approximated. The mean value for serum albumin at the onset of diuresis was 3.1 Gm. per hundred cubic centimeters (standard deviation = ± 0.2 Gm.) and the mean value for serum globulin was 4.1 Gm. (standard deviation = ± 0.7 Gm.). The level of albumin is near the transition point between that of the group of patients with ascites and that of the group without ascites, as illustrated in figure 2.

It is seen that, particularly in those patients (except patient 6) who improved and who had complete loss of ascites, the level of serum albumin steadily rose to normal. The rise in serum albumin accompanying diuresis does not necessarily indicate a causal relationship, since both might reflect improved hepatic function. However, the rise in serum albumin, which would produce a higher osmotic pressure in the blood, would of itself tend to promote diuresis.

SUMMARY AND CONCLUSIONS

Of 61 patients with cirrhosis of the liver, 54 had an abnormal albumin-globulin ratio on admission to the hospital. These data confirm the reports of other authors.

The prognosis as to duration of life becomes increasingly grave as the level of serum albumin decreases. The levels of the serum globulin and the serum total protein have no such prognostic significance.

There is a direct correlation between the level of the serum albumin and the clinical course. Clinical improvement is associated with a rise in serum albumin toward normal. In instances of clinical failure there is no sustained rise.

The level of serum albumin is significantly lower in patients with ascites than in those without ascites.

Diuresis is associated with a rise in serum albumin. The mean value for serum albumin at which diuresis occurs is 3.1 Gm. per hundred cubic centimeters (standard deviation = ± 0.2 Gm.).

From the data presented, it appears that a reduction in serum albumin is an essential factor in the formation of ascites.

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SERUM PROTEINS IN CIRRHOSIS OF THE LIVER

II. NITROGEN BALANCE STUDIES ON FIVE PATIENTS

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It has not been clear from clinical studies whether the low values for serum albumin associated with cirrhosis of the liver are due to altered protein synthesis or to protein starvation, caused either by low protein intake or by faulty assimilation. Peters and Eisenman [1] ascribed such hypoalbuminemia to insufficient protein intake. Myers and Keefer,[2] however, observed 2 patients with cirrhosis of the liver and ascites and suggested that the hypoproteinemia was due to altered blood protein synthesis associated with the diminished hepatic function. The low serum albumin levels of their patients were unchanged during long periods of high protein feeding, although normal fecal nitrogen values during these periods indicated that the protein was assimilated. Grabfield and Prescott [3] reported a positive nitrogen balance for 1 patient who had cirrhosis of the liver without ascites, but with normal blood proteins.

According to Ling [4] and Liu, Chu, Wang and Chung,[5] when patients with starvation hypoproteinemia are fed 1 to 2 Gm. of protein per kilogram of body weight they respond with a significant rise in serum albumin within ten to twenty days.

From the Research Service, 1st Medical (Columbia) Division, Welfare Hospital, and the Department of Medicine, Columbia University College of Physicians and Surgeons.

1. Peters, J. P., and Eisenman, A. J.: The Serum Proteins in Diseases Not Primarily Affecting the Cardiovascular System or Kidneys, Am. J. M. Sc. **186**: 808, 1933.

2. Myers, W. K., and Keefer, C. S.: Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver, Arch. Int. Med. **55**:349 (March) 1935.

3. Grabfield, G. P., and Prescott, B. S.: Nitrogen and Sulfur Metabolism in Bright's Disease: VIII. Effect of Ingestion of Urea on Nitrogen Excretion and Sulfur Partition in Nephrosis, Glomerulonephritis and Cirrhosis of Liver, Arch. Int. Med. **59**:823 (May) 1937.

4. Ling, S. M.: Changes in Serum Proteins in Undernutrition, Chinese J. Physiol. **5**:1, 1931.

5. Liu, S. H.; Chu, H. I.; Wang, S. H., and Chung, H. L.: Effect of Level and Quality of Protein Intake on Nitrogen Balance, Plasma Proteins and Edema, Chinese J. Physiol. **6**:73, 1932.

Madden and Whipple [6] found that when normal dogs were maintained on a low protein diet and subjected to prolonged plasmapheresis the serum proteins could be markedly reduced. However, the feeding of adequate protein quickly restored the low blood protein levels to normal.

Weech and Goettsch [7] found that regeneration of blood protein was rapid in normal dogs whose protein stores were depleted for relatively short periods (twenty-one days) by low protein feeding. However, blood protein regeneration was impaired when protein starvation was continued for longer periods (eighty-five days). "Extreme fatty infiltration and distended bile canaliculi" were observed in the livers of such animals. The authors suggested the possibility that there might be associated with these microscopic changes disturbances in hepatic function which could account for the abnormally slow regeneration of blood protein.

There is ample evidence that injury to the liver may affect protein metabolism. Kerr, Hurwitz and Whipple [8] have shown that in dogs with Eck fistulas or in those poisoned with chloroform or phosphorus the ability to form blood protein after plasmapheresis is impaired. Knutti, Erickson, Madden, Rekers and Whipple [9] recently confirmed this observation with respect to the Eck fistula dog. Furthermore, poisoning with carbon tetrachloride decreases the serum albumin.[10] Other authors have observed hypoalbuminemia in such diseases of the liver as acute catarrhal jaundice and toxic hepatitis,[11] and in simple atrophy of the liver in a child.[12]

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6. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization, Physiol. Rev. **20**:194, 1940.

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From our own observations on patients with cirrhosis of the liver, it seems unlikely that the low serum albumin values in cases of this disease are due to simple protein starvation, although in many instances the diet before admission to the hospital may have been deficient in meat and dairy products.[13] Furthermore, after admission to the hospital many patients were fed 1.5 to 2 Gm. of protein per kilogram of body weight daily for weeks or months without the occurrence of a significant rise in the level of the serum albumin. These patients did not have diarrhea. Such findings are quite different from those for patients with starvation hypoproteinemia.[14] A further distinguishing feature between starvation hypoalbuminemia and the hypoalbuminemia associated with cirrhosis of the liver is that in the latter disease the globulin level may be high whereas in starvation hypoalbuminemia the globulin level is usually normal.

In order to determine whether the hypoalbuminemia occurring in cirrhosis of the liver is due to insufficient protein intake, to faulty gastrointestinal absorption or to faulty synthesis of serum albumin, nitrogen balance was studied in 5 patients with cirrhosis of the liver and ascites. The results show that these patients with hypoalbuminemia are in positive nitrogen balance, although there is no associated rise of serum albumin, and suggest impaired synthesis of serum albumin.

METHOD

Five patients with cirrhosis of the liver, ascites and hypoalbuminemia were studied. The ascites did not require paracentesis. All patients were confined to bed during the study periods. For patients 1, 2 and 3 (table 1) balance studies were made at approximately two week intervals for two, two and one month, respectively. For patients 4 and 5 (table 2) urinary nitrogen was determined daily for thirty-two and twenty-five days, respectively, the stools being collected for two forty-eight hour and two seventy-two hour periods in each case. The average of these determined values for fecal nitrogen was considered the daily fecal nitrogen content during the entire period of study (table 3). Urine was collected under xylene, and stools were collected in concentrated sulfuric acid. Determinations of urinary nitrogen were done in duplicate and determinations of fecal nitrogen were done in triplicate. All results were checked within 1 per cent.

The daily diets, which were composed of fresh meats, fruits and vegetables, dairy products and bread, contained approximately 280 Gm. of carbohydrate, 100 Gm. of fat and 100 Gm. of protein. A foreperiod of four to six weeks on such a diet preceded the balance studies in each case. The diets were weighed before and after meals and the protein content computed from tables.[15] The

13. Patek, A. J., Jr., and Post, J.: Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex, J. Clin. Investigation **20**:481, 1941.

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TABLE 1.—*Nitrogen Balance in Three Patients with Cirrhosis of the Liver and Ascites*

Patient No.	Date	Nitrogen Intake, Gm.	Urinary Nitrogen, Gm.	Fecal Nitrogen, Gm.	Nitrogen Balance, Gm.	Serum Albumin, Gm. per 100 Cc.	Serum Globulin, Gm. per 100 Cc.	Serum Nonprotein Nitrogen, Mg. per 100 Cc.	Comment
1	4/ 2/40	18.4	11.6	0.7	+ 6.1	2.8	5.4	35	Negro aged 45; history of intensive antisyphilitic treatment and alcoholism; severe jaundice and moderate ascites of 4 months' duration; hepatosplenomegaly; bromsulphalein dye retention 60 per cent in one-half hour; chronic bilateral pyelonephritis with albuminuria; slow diuresis
	4/ 3/40	16.9	11.7	0.7	+ 4.5				
	4/14/40*	14.9	8.6	0.9	+ 5.4				
	4/15/40*	15.9	6.6	0.9	+ 8.4				
	4/18/40	....	....	...	.....	3.0	5.2	39	
	5/30/40	18.5	13.3	1.7	+ 3.5				
	5/31/40	15.7	12.7	1.7	+ 1.3				
	6/ 1/40	....	....	...	.....	2.4	4.3	38	
2	3/23/40	....	....	...	.....	2.8	4.0	35	White woman aged 50; marked alcoholism, with one episode of delirium tremens (November 1939); moderate ascites of 2 months' duration; many spider angiomas; bromsulphalein dye retention 60 per cent in one-half hour; urine normal; slow diuresis
	3/27/40	18.7	6.4	0.3	+12.0				
	3/28/40	20.0	7.7	0.3	+12.0				
	4/ 2/40	18.1	7.8	1.2	+ 9.1	2.5	4.7	23	
	4/ 3/40	17.9	8.8	1.2	+ 7.9				
	4/ 8/40	....	...	...	.....	2.7	4.4	23	
	4/14/40*	14.2	8.5	1.4	+ 4.3				
	4/15/40*	13.5	8.8	1.4	+ 3.3				
	4/18/40	....	...	...	.....	3.0	4.4	29	
	5/ 2/40	....	...	...	.....	3.4	4.5	30	
	5/30/40	19.5	12.9	2.5	+ 4.1				
	5/31/40	19.6	12.9	2.5	+ 4.2				
	6/ 4/40	....	....	...	.....	3.2	3.7	27	
3	3/14/40	....	....	...	.....	3.2	3.1	28	White man aged 45; history of intensive antisyphilitic treatment; episode of hematemesis 2 months before study began treated with 3 transfusions, with marked improvement; moderate ascites of 1 month's duration; many spider angiomas; esophageal varices revealed by roentgen ray examination; bromsulphalein dye retention 30 per cent in one-half hour; urine normal; slow diuresis
	3/15/40	20.0	11.4	0.9	+ 7.7				
	4/ 2/40	20.3	10.9	2.4	+ 7.0	3.1	3.2	27	
	4/ 3/40	18.2	11.6	2.4	+ 4.2				
	4/ 8/40	....	....	...	.....	3.4	3.5	27	
	4/14/40*	16.5	3.4	0.9	+12.2				
	4/15/40*	15.9	7.8	0.9	+ 7.2				
	4/18/40	....	....	...	.....	3.0	3.8	33	

* No brewers' yeast was administered.

TABLE 2.—*Nitrogen Balance in Two Patients with Cirrhosis of the Liver and Ascites*

Date	Patient 4 *						Patient 5 †					
	Nitrogen Intake, Gm.	Urinary Nitrogen, Gm.	Nitrogen Balance,‡ Gm.	Serum Albumin, Gm. per 100 Cc.	Serum Globulin, Gm. per 100 Cc.	Serum Nonprotein Nitrogen, Mg. per 100 Cc.	Nitrogen Intake, Gm.	Urinary Nitrogen, Gm.	Nitrogen Balance,§ Gm.	Serum Albumin, Gm. per 100 Cc.	Serum Globulin, Gm. per 100 Cc.	Serum Nonprotein Nitrogen, Mg. per 100 Cc.
9/ 5/40	16.1	9.7	+ 5.0	...	...	..	18.4	11.5	+ 5.0	3.2	4.2	25
9/ 6	13.5	14.2	— 3.1	...	...	..	17.3	11.7	+ 4.0			
9/ 7	12.0	13.7	— 3.1	2.8	3.9	23	16.8	10.6	+ 4.6			
9/ 8	13.5	12.1	0	...	...	..	18.9	10.6	+ 6.7			
9/ 9	13.3	15.6	— 3.7	...	...	..	15.4					
9/10	15.6	9.0	+ 5.2	...	...	..	16.6	12.2	+ 2.8			
9/11	19.3	12.1	+ 5.8	...	...	..	12.8	9.5	+ 1.7			
9/12	18.1	11.6	+ 5.1	...	...	..	16.9	9.6	+ 5.7			
9/13	18.3	12.3	+ 4.6	...	...	..	16.2	8.6	+ 6.0			
9/14	19.9	10.2	+ 8.3	2.7	4.0	27	14.4	10.0	+ 2.8			
9/15	18.6	11.4	+ 5.8	...	...	..	17.3	15.4	+ 0.3	3.2	4.3	27
9/16	19.4	6.7	+11.3	...	...	..	14.7	10.7	+ 2.4			
9/17	14.6	11.4	+ 1.8	...	...	..	16.5	10.7	+ 4.2			
9/18	18.9	16.3	+ 1.2	...	...	..	18.5	12.2	+ 4.7			
9/19	19.4	15.5	+ 2.5	...	...	..	14.5	12.1	+ 0.8			
9/20	16.7	8.5	+ 6.8	...	...	..	17.7	10.3	+ 5.8			
9/21	17.0	11.7	+ 3.9	...	...	..	16.3	10.0	+ 4.7			
9/22	20.9	11.4	+ 8.1	...	...	..	20.3					
9/23	17.2	13.3	+ 2.5	2.4	3.6	28	17.7	12.9	+ 2.2	3.3	3.4	29
9/24	19.3	11.3	+ 6.9	...	...	..	17.4	11.1	+ 4.7			
9/25	18.6	11.6	+ 5.6	...	...	..	21.0	13.9	+ 5.5			
9/26	19.1	12.4	+ 5.3	...	...	..	16.5	12.6	+ 2.3			
9/27	23.8	11.3	+11.1	...	...	..	19.0	13.9	+ 3.5			
9/28	19.4	11.7	+ 6.3	...	...	..	17.6	9.9	+ 6.1			
9/29	21.8	13.2	+ 7.2	...	...	..	21.4	10.7	+ 9.1			
9/30	18.5	9.2	+ 7.9	...	...	..	19.2	11.8	+ 5.8			
10/ 1	15.7	12.7	+ 1.6	...	...	..	18.1	11.8	+ 4.7	2.6	4.4	22
10/ 2	18.2	13.4	+ 4.0	2.5	3.7	23						
10/ 3	19.0	9.0	+ 7.6									
10/ 4	17.8	17.4	— 0.6									
10/ 5	17.8	14.3	+ 2.1									
10/ 6	14.3	10.1	+ 2.8									

* A white man aged 50 with a history of extreme alcoholism, one episode of severe peripheral neuritis 6 months before study was begun, appreciable ascites of 3 months' duration, severe jaundice, hepatosplenomegaly, numerous spider angiomas, retention of 80% of an injection of bromsulphalein, normal urine and slow diuresis.

† A Negress aged 36 with a history of extreme alcoholism, severe ascites of 3 months' duration, bromsulphalein dye retention 40 per cent in one-half hour, normal urine and slow diuresis.

‡ Average excretion of fecal nitrogen = 1.4 Gm. per 24 hours (see table 4).

§ Average excretion of fecal nitrogen = 1.6 Gm. per 24 hours (see table 4).

factor 1/6.25 was used for conversion to nitrogen. The accuracy of the food tables used was checked by chemical analyses of six sample diets (table 4). A sample diet was placed in a Waring mixer for two to three hours, and portions of the resulting homogeneous mixture were analyzed in triplicate and checked within less than 1 per cent. Except where otherwise noted the patients received 40 to 60 Gm. of brewers' yeast daily, in addition to the diet. The nitrogen content of this yeast was determined as 8.5 per cent. The micro-Kjeldahl method for nitrogen determination was employed throughout the studies.

TABLE 3.—*Excretion of Fecal Nitrogen by Patients 4 and 5*

	Date	Fecal Nitrogen, Gm.
Patient 4	9/14 - 9/16	2.0
	9/21 - 9/23	3.0
	9/29 -10/ 2	3.9
	10/ 5 -10/ 8	5.4
	Average	1.4 Gm. per 24 hr.
Patient 5	9/ 6 - 9/ 8	3.4
	9/14 - 9/16	4.4
	9/21 - 9/24	4.5
	9/29 -10/ 2	3.6
	Average	1.6 Gm. per 24 hr.

TABLE 4.—*Comparison of the Calculated and Determined Nitrogen Contents of Six Sample Diets*

Calculated Amount of Nitrogen	Determined Amount of Nitrogen
4.10 Gm.	4.10 Gm.
7.63 Gm.	8.50 Gm.
3.18 Gm.	3.19 Gm.
5.56 Gm.	6.87 Gm.
3.18 Gm.	3.23 Gm.
6.43 Gm.	7.63 Gm.

RESULTS

The data for the 5 patients studied (tables 1 through 4) show that relatively normal amounts of nitrogen, 0.3 to 2.5 Gm. per twenty-four hours, were being lost in the stools. Therefore it is concluded that the patients had no defect in the absorption of protein from the intestinal tract. These results confirm those of Myers and Keefer.[2] Furthermore, they indicate that the patients were in positive nitrogen balance, since the nitrogen intake exceeded the nitrogen output. Such findings indicate that the patients were in a state of partial protein depletion, as suggested by Peters and Eisenman.[1] However, since the nonprotein nitrogen of the blood and the serum proteins, particularly the serum albumin, remained essentially unchanged and since there was no constant drain

of protein by abdominal paracentesis, it appears that nitrogen was being stored, probably as body protein. In other words, there is no apparent tendency for the serum proteins to reflect this positive nitrogen balance.

This ability of the body to retain protein from the food and its failure to synthesize serum proteins may be illustrated by the following examples:

Patient 5 showed a rise in serum albumin from 3.2 to 3.6 Gm. per hundred cubic centimeters during the period of four weeks, an increase of approximately 13 Gm. of circulating albumin. However, during this time the patient retained the equivalent of 657 Gm. of protein as nitrogen. Patient 4 showed a slight decrease in the serum albumin from 2.8 to 2.5 Gm. per hundred cubic centimeters during the four and a half weeks of study, but retained the equivalent of 849 Gm. of protein as nitrogen.

This type of balance pattern is quite different from that seen in cases of nutritional hypoproteinemia. In the latter the level of the serum proteins, particularly that of the serum albumin, rises fairly rapidly when protein is fed.[14] Whipple[16] has shown that there normally exists a ready exchange between the body protein stores and the blood proteins and that the latter are reduced only after body protein stores are depleted. When protein is made available to the animal, the first response is a rise in the blood protein level. It appears from our data that in the patient with cirrhosis of the liver the restoration of the serum albumin to normal is delayed when protein is made available. The retained nitrogen is apparently converted to body protein and not to blood protein, a change which suggests faulty synthesis of serum albumin.

SUMMARY AND CONCLUSIONS

Nitrogen balance studies were made on 5 patients with cirrhosis of the liver, ascites and reduced serum albumin.

Although the patients remained in positive nitrogen balance during the periods of high protein feeding, there was no correlated rise in the level of the serum albumin. In this respect these patients differ from persons with simple protein starvation.

The data recorded here indicate that patients with cirrhosis of the liver absorb and retain food protein. The evidence suggests that the mechanism for the synthesis of serum albumin is impaired.

Miss Josephine Henneberger gave technical assistance.

16. Whipple, G. H.: Protein Production and Exchange in the Body, Including Hemoglobin, Plasma Protein and Cell Protein, Am. J. M. Sc. **196**:609, 1938.

TORULA MENINGITIS

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We report a case of fatal torula meningitis complicating Hodgkin's disease.

REPORT OF A CASE

The patient was an American-born man aged 39 who was referred to the Collis P. Huntington Memorial Hospital for treatment of "reticulum cell sarcoma" of the neck and the mediastinum. This diagnosis had been made at another hospital on the basis of a biopsy of a right supraclavicular node and a widened mediastinal shadow in a roentgenogram. Symptoms of easy fatigability, loss of appetite, susceptibility to colds and rheumatoid pains had been present for about one year, but the most distressing and urgent symptom, severe occipitofrontal headaches, was of shorter duration, a little over one month. Projectile vomiting had accompanied some of these attacks of headache, and an irregular fever, with a temperature up to 103 F., had been noted during one of these occasions. The only point of possible interest in the past history was a deep injury to the nose resulting from a fall on an upright stick in 1933.

At the time of admission, the patient was well developed but had evidently lost a great deal of weight. There was no marked enlargement of peripheral lymph nodes. Mediastinal tumor was suggested by a widening and an increased density of the upper portion of the mediastinum, detectable both by percussion and in the roentgenograms. The teeth were carious, and the tonsils had a granular appearance but were not enlarged. Neurologic examination gave no clue to his headaches. The reflexes were sluggish. Impairment of vision was striking, the patient being able to read only large newspaper print. Bilateral papilledema, with an elevation of 1 D., and wasting of interosseous muscles and of the thenar eminences of the hands were present. Except for leukocytosis, with a white cell count of 20,350 per cubic millimeter, the blood count was not remarkable. Roentgenograms showed diffuse calcification in the choroid plexuses. A lumbar puncture disclosed fluid under normal pressure, with no unusual cell content, a negative Wassermann reaction and a colloidal gold curve of 0001121100. Supervoltage radiation was given to the anterior portions of the mediastinum and the abdomen in equal amounts of 800 r, with relief of nausea and vomiting. Shortly thereafter, 740 r directed to the side of the head through a 15 by 15 centimeter portal seemed to lessen the severity of the headaches, and there were some improvement in vision and reduction of papilledema.

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For three months the patient did not suffer any appreciable discomfort, but weakness and headaches gradually returned. The headaches became progressively worse and were most troublesome at night. Projectile vomiting in the morning became distressing. Because of the severe headaches and vomiting, the patient was admitted to the hospital a second time, nine months after his first admission and radiation treatments. At this time examination revealed the same physical findings noted previously, with additional nystagmoid movements on looking to the right, as well as some loss of coordination. Lymph nodes in the right cervical chain were definitely enlarged, and the spleen was palpable. Lumbar puncture revealed normal dynamics of the cerebrospinal fluid, an increase in the cell count to 196 per cubic millimeter, a total protein content of 200 mg. per hundred cubic centimeters and a colloidal gold curve of 0000112110. A culture of the fluid was negative for growth, and a guinea pig inoculated with the fluid failed to show any lesions after twenty days. Histologic examination of a cervical node disclosed Hodgkin's disease. In view of the subjective improvement following the first supervoltage roentgen irradiation to the head, a second series of twelve daily treatments, totaling 800 r, was given. After the roentgen irradiation there was again some relief of the headaches but less than that which followed the first irradiation nine months before. However, an examination of cerebrospinal fluid showed a reduction of the cell count to 74 cells per cubic millimeter, with a further reduction one month later to 22 cells per cubic millimeter. The other findings for the cerebrospinal fluid were the same as on the first admission, and cultures did not show any growth. In addition, 1,200 r supervoltage radiation was directed to the mediastinum and 600 r high voltage radiation to the right supraclavicular region. This was followed by reduction in size of the lymph nodes and the spleen. The patient felt improved and returned home.

After this second series of radiation treatments, the relief from symptoms was less complete and of shorter duration, and the patient was readmitted, after a five month interval, for what proved to be his last series of treatments. Examination at this time disclosed his increasingly poorer condition, for he was completely disoriented, emaciated and weak. The spleen was definitely enlarged, as were the lymph nodes in the left supraclavicular area. The left pupil was dilated, and ophthalmoscopic examination revealed choroiditis on that side. An encephalogram disclosed nothing remarkable. Lumbar puncture still showed normal dynamics, but the cell count had increased to 38 per cubic millimeter of cerebrospinal fluid and continued to rise to 181, as shown in the last examination, done one month later. Otherwise, the cerebrospinal fluid was unchanged, and cultures were still negative for growth. The patient was given 500 r supervoltage radiation to his head in two treatments with no noticeable effect. He also received 600 r high voltage radiation to the left supraclavicular area and 900 r supervoltage radiation to the left upper portion of the abdomen, including the spleen. There was a reduction in the size of the lymphoid tumors, but otherwise no improvement. The blood picture, which had been normal on entry, was characterized by a red cell count of 2,350,000 per cubic millimeter and a hemoglobin concentration of 44 per cent (Sahli); the progressive anemia continued in spite of a transfusion of 500 cc. of citrated blood. The leukocytes had remained fairly constant, around 10,000 per cubic millimeter, with a differential count of 81 per cent neutrophils, 10 per cent lymphocytes, 7 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils, but the leukocytes were reduced to 4,500 per cubic millimeter, with a comparable differential count. The results of urinalysis had been essentially negative but began to show terminal pyuria. The decline was rapid, with development of coma during the last few days, and death occurred from respira-

tory failure, eighteen months after the onset of severe neurologic symptoms and thirty months after the onset of symptoms referable to the known lymphomatous lesions.

To summarize, the clinical course had two distinct aspects. The first was malignant lymphoid tumor which involved the cervical and mediastinal nodes, with weakness, loss of weight and vague symptoms that began two and a half years before death. The second, more striking, group of symptoms was related to an intracranial involvement of only eighteen months' duration. In the absence of definite evidence to the contrary and in spite of its rarity, the entire clinical picture was ascribed to the proved malignant lymphoid tumors.

At necropsy two distinct gross pathologic entities were found: (*a*) a slight inflammatory reaction in the meninges of the brain, spinal cord and ependyma and (*b*) discrete fibrous and granular nodules in various organs, interpreted as evidence of Hodgkin's disease.

The dura of the brain was normal, but the leptomeninges of the brain were everywhere edematous and slightly cloudy with more definite opacity over the principal fissures and over the brain stem. The brain substance was normal in every respect, there being no evidence of extension of inflammation from the pia-arachnoid. Uniform, finely granular ependymitis was present in all the ventricles; the choroid plexuses were firm and covered by a dull white membrane. The dura of the entire cord was attached to the pia by fairly tenacious, fine adhesions. The substance of the cord was normal.

Microscopic examination of the brain and cord disclosed diffuse leptomeningitis, most exuberant around the large vessels, consisting of a granulomatous reaction to a yeastlike organism, Torula. Usually the response excited by the presence of these organisms is simply a migration of endothelial leukocytes, although lymphocytes, eosinophils and polymorphonuclears may play a minor role. In our case only rare lymphocytes were seen among the large numbers of endothelial leukocytes which actively phagocytosed the organism. Large giant cells formed by the fusion of leukocytes and filled with torulas, many of which were partly degenerated, gave a foamy appearance to the exudate. The infection had extended along some of the small vessels into the substance of the brain and had invaded adjacent brain tissue in a few minute foci. Some of these foci had undergone dissolution, which produced microscopic cavities. A few of the spinal nerves were likewise invaded by the organism.

Although large numbers of endothelial leukocytes were present, there were almost as many torula organisms lying free in the meshes of the edematous meninges. They were for the most part well preserved, and a few were in the process of budding, but several showed slight changes in contour and staining properties that suggested early degeneration. Aside from the migration of endothelial leukocytes and a few lymphocytes, there had been no appreciable response to the presence of the organism. Only slight thickening of the fibrous elements of the leptomeninges, without distinct evidence of proliferation, was noted.

The concomitant pathologic process, consisting of discrete granular and fibrous lesions, was evident (*a*) in the cervical, supraclavicular, axillary, inguinal and pulmonary hilar lymph nodes, producing moderate enlargement and uniform structure; (*b*) throughout the parenchyma of both lungs as granular, but partially fibrous, nodules 1 to 2 cm. in diameter; (*c*) in the center of the left lobe of the liver as a single, solitary nodule with irregular streaked edges, a lesion more characteristic of scirrhous carcinoma than of Hodgkin's disease; (*d*) in a large,

530 Gm. spleen as numerous, slightly elevated, granular, yellow nodules averaging 2.5 cm. in diameter and separated by bands of dark purple pulp, and (*e*) in the lumbar vertebral marrow as scattered yellowish, nondescript foci under 1 cm. in diameter.

Histologically, these lesions differed from those observed during the second biopsy, made at the Huntington Memorial Hospital six months before death, by a greater predominance of fibrosis and reduction in cells, chiefly lymphocytes, eosinophils, plasma cells, multinuclear giant cells and rare Sternberg cells. The

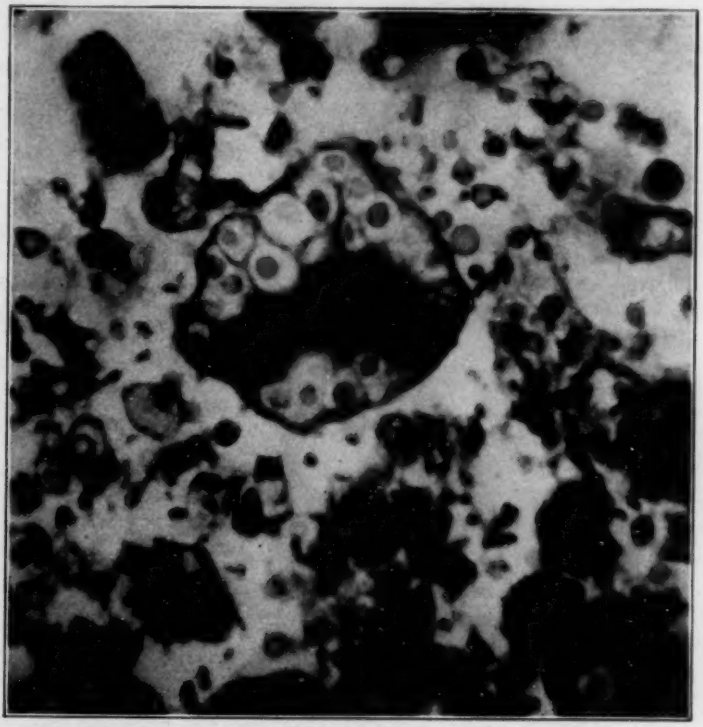

Fig. 1.—A section of the leptomeninges showing a large giant cell with multiple, deeply staining, clumped nuclei in the center and engulfed torula organisms in the periphery. Torulas are also visible lying free in tissue spaces, as well as in single phagocytes. × 600.

lesions most characteristic of Hodgkin's disease were in the lymph nodes, liver, spleen and bone marrow.

Some of the nodules in the lung parenchyma appeared less typical, and, in view of the recorded cases of torula lesions having been misinterpreted as Hodgkin's disease, and also because the respiratory tract is reported to be the portal of entry for the organism, a more careful study was made of these lesions. Many sections stained by the Gram-Weigert method and with phosphotungstic acid

hematoxylin and hematoxylin and eosin were fruitlessly searched for the organism, although the appearance of a few vacuolated, phagocytic cells suggested its presence. In connection with his aid in the preparation of the monograph by Stoddard and Cutler,[1] Dr. S. Burt Wolbach had found Masson's aniline blue stain most helpful in demonstrating Torula. With the use of this stain, organisms could be seen in a few phagocytic cells in the periphery of the pulmonary nodules. Their identity was confirmed by Dr. Shields Warren,[2] so that we can confidently say that the pulmonary lesions are, at least in part, a reaction to the yeast and the lung may

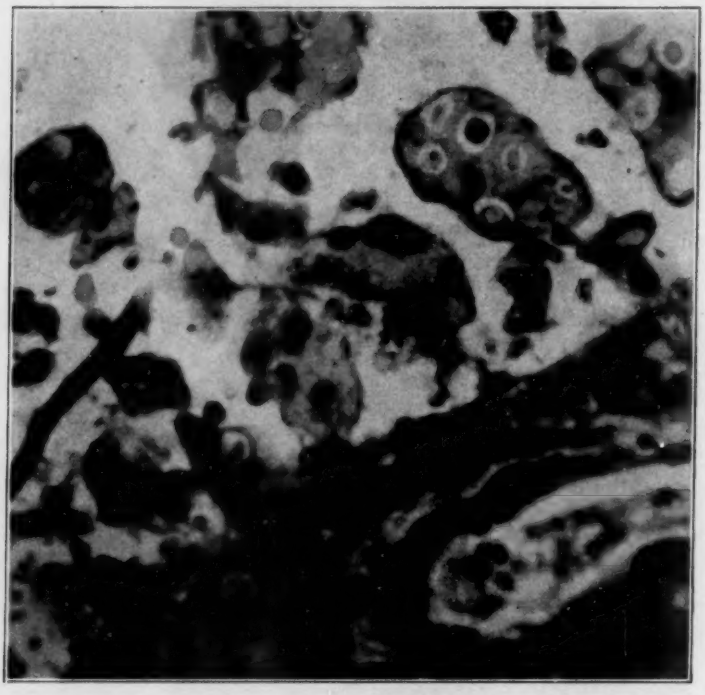

Fig. 2.—Perivascular infiltration of phagocytic cells and organisms. × 600.

have been a portal of entry in this case. The scarcity of organisms in parenchymatous organs has been ascribed to the exuberant reaction and fibroblastic proliferation that obscures them and also causes their degeneration. More often Torula produces a large caseous lesion in the lung, but Rappaport and Kaplan[3] reported multiple small fibrous foci similar to those seen in this case.

1. Stoddard, J. L., and Cutler, E. C.: Torula Infection in Man, Monograph 6, Rockefeller Institute for Medical Research, 1916.

2. Pathologist to the Collis P. Huntington Memorial Hospital.

3. Rappaport, B. Z., and Kaplan, B.: Generalized Torula Mycosis, Arch. Path. **1**:720 (May) 1926.

COMMENT

The first inclusive and useful report of torula meningitis in man was made by Stoddard and Cutler,[1] in 1916. In a later (1931) extensive review of the subject, Freeman [4] accepted 43 cases as authentic. Levin [5] reviewed the subject in 1937 and added 14 cases reported in the literature after Freeman's article, as well as 2 cases of his own. Binford [6] (1930) tabulated 14 cases reported subsequent to Levin's review and added 1 case of his own. Wade and Stevenson [7] recently (1941) reported 1 case, and Stiles and Curtiss [8] added still another. To a total of 77 cases recorded in the literature we add a seventy-eighth. One feature notable in a review of the subject is the frequency with which Hodgkin's disease and torula meningitis are associated. Wade and Stevenson [7] cited 4 cases of coincident lymphomatosis, and Mallory [9] stated that he had personally observed 5 instances. In 7 of these 9 cases the lymphomatous lesions were those of Hodgkin's disease. Mallory [9] further referred (1934) to an unpublished manuscript mentioning about a dozen cases of associated torula infection and Hodgkin's disease, although we find no report to date containing this number of cases. Mallory [9] remarked: "The coincidence is much too striking to be purely a matter of chance. It is not so close as the coincidence of tuberculosis and Hodgkin's disease, but it certainly approaches it."

Torula, a yeastlike organism, is widely distributed throughout nature and is only rarely pathogenic for man. It differs from a true yeast in that it does not produce endospores and forms mycelium only under certain cultural conditions (Ball [10]). The organisms were, for the most part, well preserved in the leptomeninges in our case. Some were seen in the process of budding, which is the characteristic method of reproduction. They were 2 to 14 microns in diameter, with a central round body and a mucoid capsule that did not take ordinary stains but was apparent because of its distinct outer membrane. Although there are vagaries of staining, Mallory's aniline blue stains the organisms orange

4. Freeman, W.: Torula Infection of the Central Nervous System, J. f. Psychol. u. Neurol. **43**:236, 1931.

5. Levin, E. A.: Torula Infection of the Central Nervous System, Arch. Int. Med. **59**:667 (April) 1937.

6. Binford, C. H.: Torulosis of the Central Nervous System: Review of Recent Literature and Report of a Case, Am. J. Clin. Path. **11**:242, 1941.

7. Wade, L. J., and Stevenson, L. D.: Torula Infection, Yale J. Biol. & Med. **13**:467, 1941.

8. Stiles, W. W., and Curtiss, A. N.: Torula Meningoencephalitis, J. A. M. A. **116**:1633 (April 12) 1941.

9. Torula Meningitis: Lymphoblastoma, Hodgkin's Type, Cabot Case 20241, New England J. Med. **210**:1291, 1934.

10. Ball, H. A.: Human Torula Infections: Review; Report of Cases, California & West. Med. **32**:338, 1930.

and the capsule blue. There appear to be several types or strains, which vary in size, in ease of cultivation and in pathogenicity for animals.

The effect of the organism, judging from reports in the literature, is more commonly the production of focal granulomatous lesions that grossly resemble those of tuberculosis. In our case the involvement was more diffuse, with edema of the leptomeninges and a cellular exudate consisting primarily of endothelial leukocytes that engulfed the organism and often coalesced to form giant cells. The lymphocytes, plasma cells and granulocytes, often reported present, were less prominent in our case. There was some extension of reaction along vascular sheaths into the brain substance but no evidence of the marked cystic process that has been described by some as giving a grossly visible "soap bubble" effect. The variability in pathologic processes has been related to the strain of organism; those with thicker capsules are supposedly accompanied by more cyst formation, while the thinner-capsuled organisms incite more of a microglial reaction. The organism appears to have little if any toxic action but acts more as a foreign body than as an infectious agent.

Little is known of the clinical course, especially in its early stages, since the condition is rarely diagnosed until meningitis is well established. The portal of entry is believed to be the respiratory tract, but the interval that precedes the onset of manifestations of cerebral involvement is not known. Signs and symptoms of increased intracranial pressure have an insidious onset but become progressively more severe, with short periods of remission. The first symptom is severe headache, which is later accompanied by projectile vomiting and increasing weakness. Coma or occasional convulsions occur late, and death is usually due to respiratory failure. Spread of the disease is by embolic dissemination, and organisms may be cultivated from the blood and the urine. Although torula organisms have been found in almost every organ at one time or another, such involvement, with rare exceptions, is usually secondary to the meningitis.

The possible presence of torula meningitis must be considered in all cases of slowly progressive meningeal irritation and increased intracranial pressure after the diagnosis of tuberculosis, syphilis and tumor of the brain have been excluded. The greatest help is from examination of the spinal fluid, which may appear clear, turbid or gelatinous, with an increase in pressure up to 700 cm. of water. The cell count is increased, with a predominance of lymphocytes. Torulas are often mistaken for red blood cells or lymphocytes but may be observed best in a hanging drop preparation and are most distinctive when seen engulfed by phagocytic cells. The proteins are increased, and the Pandy reaction for globulins is positive. The colloidal gold curve shows a midzone rise or occasionally may be of the paretic type. Culture of organisms may be

difficult, but growth should occur in carbohydrate mediums at room temperature. Cultures were repeatedly negative for Torula in our case and also in another case recently studied by Dr. Warren. If one judges by the case reports in the literature, the demonstration of organisms by culture is more difficult in cases in which the infection is of longer duration. Two of the most recently reported cases are examples of this. Binford [6] reported a case with a clinical course similar to that in ours and in which only 1 of 7 centrifuged specimens of cerebrospinal fluid yielded the organism either by culture or by microscopic examination, although injections into animals were successfully made with 3 different samples of fluid in which no organisms were seen or cultured. The case reported by Stiles and Curtiss [5] is the exact converse, for in it the illness ran an acute course, with death occurring on the twenty-fifth day after the onset of symptoms; the organism was cultured from the cerebrospinal fluid, as well as from the blood, from the first specimens taken at the end of the first week. Animal inoculations usually have been made intraperitoneally or intranasally into mice and rats; the guinea pig was used in our case, as well as in others reported recently.

The most definite diagnostic procedure is reported to be a biopsy of the meninges, particularly of tissue overlying a sulcus; however, care must be taken to obtain representative tissue and not the more accessible necrotic, membranous exudate in which the organisms are disintegrated and not demonstrable.

All treatment has been ineffective in 100 per cent of the cases, and death usually occurs within sixteen months after the onset of definite symptoms. The most complete therapeutic studies are accredited to Shapiro and Neal,[11] who kept their patient alive six months after a diagnosis of torulosis was made. They expressed the belief that the most effective palliative measure is the lumbar puncture, which keeps down the increasing intracranial pressure. In their case they performed 133 punctures. They later found acriflavine in a dilution of 1:10,000 to be the only substance that was inhibitory within therapeutic limits of dosage. There have been no reports of a clinical trial, but, in view of the invariably fatal course of this disease, the physicians at the New England Deaconess Hospital decided to try it in 1 case.[12] In this case the diagnosis of torulosis was suspected by Dr. Warren on examination of necrotic membranous material removed during a suboccipital exploration and was confirmed by demonstration of the organisms in the spinal fluid by observation in a hanging drop preparation, as well as by recovery of torulas from an inguinal abscess of a guinea pig inoculated

11. Shapiro, L. I., and Neal, J. B.: Torula Meningitis, Arch. Neurol. & Psychiat. **13**:174 (Feb.) 1925.

12. The patient had been admitted to the New England Deaconess Hospital in the service of Dr. G. H. Horrax, of the Lahey Clinic.

intraperitoneally. However, the patient was already moribund when the treatment was started, and no response was observed to daily intrathecal administration of 42 cc. of acriflavine hydrochloride in a dilution of 1 : 10,000 after removal of 60 cc. of spinal fluid for seven days just before death. It would seem advisable to try this only known therapeutic possibility in a case in which this invariably fatal disease is in an earlier stage.

SUMMARY

The characteristic features of this case of torula leptomeningitis are the insidious onset and the intermittent but progressive course, going on to a fatal termination. The increasing intracranial involvement caused the following consecutive manifestations: severe headaches; visual, sensory and motor disturbances; weakness; projectile vomiting; disorientation; coma, and respiratory failure.

The interesting features of this case are the occurrence of the meningitis as a complication of Hodgkin's disease and the effect of the roentgen ray treatments to the head. This is the eighth reported case of associated Hodgkin's disease and torula meningitis. The marked reduction in cells in the cerebrospinal fluid is the only positive evidence of the effect of roentgen therapy, but it does not indicate whether it was harmful or beneficial except that our patient survived eighteen months after the first severe symptoms; for the most part he was ambulatory and in relative comfort. The usual course is one of severe symptoms and death within six months.

A review of the literature indicates that a diagnosis of torulosis is to be suspected in cases of otherwise unaccountable progressive intracranial disease. Confirmation is obtained by studies of the spinal fluid, with identification of the organism either by culture or by animal inoculation. A biopsy of representative tissue from the meninges will disclose the specific lesions.

The only undoubtedly beneficial therapeutic procedure appears to be repeated withdrawals of spinal fluid to promote drainage and decrease intracranial pressure. The use of acriflavine hydrochloride intrathecally may offer some possible curative effect in cases of this invariably fatal disease.

ABSORPTION OF INTRACUTANEOUSLY INJECTED SOLUTIONS OF DEXTROSE AND SODIUM CHLORIDE

COMPARISON OF ABSORPTION TIMES FOR DIABETIC AND FOR NONDIABETIC SUBJECTS

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The behavior of dextrose and electrolytes in the tissues of persons with diabetes is of considerable interest. Seelig [1] has recently reported on the response of diabetic patients to intradermal tests with a solution of sodium chloride and 0.1 per cent dextrose. He found an increased "avidity" of the skin for dextrose in the diabetic as compared with the nondiabetic patient. McClure and Aldrich,[2] Petersen and Levinson [3] and others have reported on the intracutaneous wheal as a measure of permeability in persons with nephritis as well as in normal subjects. There has been a lack of controlled studies on cellular permeability as measured by the absorption time of various solutions in the diabetic as compared with the nondiabetic, so-called normal subject.

The results of a preliminary study, based on the method of Seelig,[1] suggested that the test may be of value, first, in studying differences in absorption in patients with uncontrolled diabetes as compared with absorption in patients whose diabetes is "controlled," and, second, in measuring the transport of fluids within the tissues. Therefore two groups of patients were studied, one group with glycosuria and an elevated value for blood sugar and a second group without glycosuria and with a more normal value for blood sugar. The results for both groups were compared with those obtained for a group of persons in apparently good health who may be considered "normal." A smaller

From the Department of Medicine, the University of Illinois College of Medicine.

1. Seelig, S. F.: Intradermal Skin Tests in Diabetes Mellitus, Guy's Hosp. Rep. **88**:210 (April) 1938.

2. McClure, W. B., and Aldrich, C. A.: Time Required for Disappearance of Intradermically Injected Salt Solution, J. A. M. A. **81**:293 (July 28) 1923. Aldrich, C. A., and McClure, W. B.: The Intradermal Salt Solution Test: II. Its Prognostic Value in Nephritis with Generalized Edema, ibid. **82**:1425 (May 3) 1924.

3. Petersen, W. F., and Levinson, S. A.: Skin Reactions, Blood Chemistry and Physical Status of "Normal" Men and of Clinical Patients, Arch. Path. **9**:151 (Jan., pt. 2) 1930.

group of patients with uncontrolled diabetes were studied at frequent intervals until they were brought under control.

The concentrations of substances chosen were the same as those reported by Seelig because they represent the average normal concentrations in the circulating blood. Because of the great difference in the osmotic pressure of an 0.85 per cent solution of sodium chloride and a 0.1 per cent solution of dextrose, the following solutions were prepared in order to determine the influence of the osmotic pressure on the rate of absorption. Each series of tests consisted of the injection of 0.5 cc. of each of these four solutions:

Solutions	Osmotic Pressure, Atmosphere
5% dextrose	6.22
0.85% sodium chloride	6.35
0.1 % dextrose	0.12
0.1 % dextrose in 0.85% sodium chloride	6.47

In order to study the absorption rates of solutions of compounds of larger molecular size and different arrangement, solutions of inulin and urea were added. The inulin was immediately discarded as being too irritating, while a 1.7 per cent solution of urea, with approximately the same osmotic tension as the 5 per cent solution of dextrose, was employed in smaller series of normal and diabetic subjects.

The technic of injections and the method of reading the end point were as follows: The needle was inserted superficially in such a manner that the lumen was visible through the skin; then 0.5 cc. of solution was injected. With slight pressure a distinct area of blanching may be clearly delineated at the site of injection. The fluid was assumed to be absorbed when the area of blanching had disappeared. This method was found to be more satisfactory than the method of palpation previously described.[2] The site of injection was the volar surface of the forearm. The same forearm was used repeatedly in tests on the same subject because differences in the absorption rates greater than those attributable to error were found in one forearm as compared with the other. McClure and Aldrich [2] have previously reported differences in the absorption rates in the upper and the lower extremity.

In order to obtain a measure of the accuracy of the technic, a series of twenty-four duplicate injections were made. In 62 per cent the error of reading was 1 minute or less, while in 75 per cent the error was 3 minutes or less.

The results of 143 observations on 45 diabetic patients and of 30 observations on 25 normal subjects have been summarized in table 1.

Charts 1, 2 and 3 were prepared in order to show both the range of variation of absorption times and the relation of the absorption

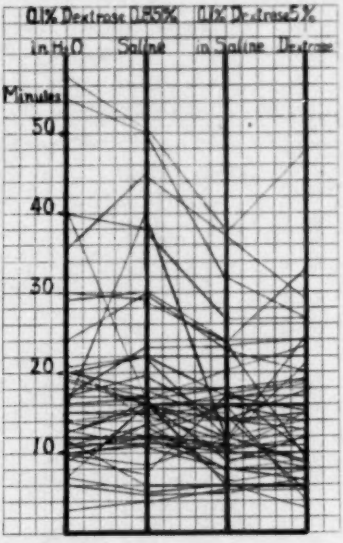

Chart 1.—Absorption times of intracutaneous injections of solutions of dextrose and sodium chloride for patients with uncontrolled diabetes.

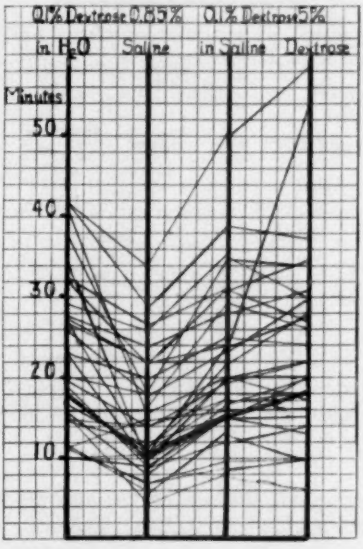

Chart 2.—Absorption times of intracutaneous injections of solutions of dextrose and sodium chloride for patients with controlled diabetes.

times of the different solutions. For each test of four solutions the actual time of absorption was recorded under the appropriate vertical column and a line drawn to connect the four observations made at one

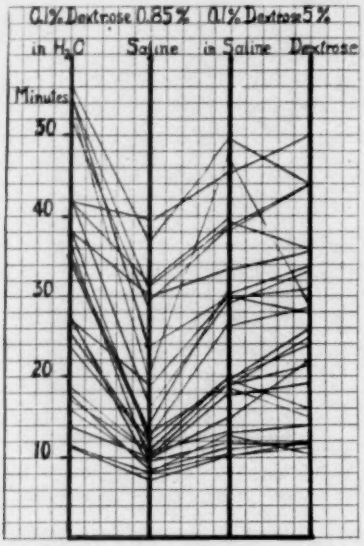

Chart 3.—Absorption times of intracutaneous injections of solutions of dextrose and sodium chloride for nondiabetic subjects.

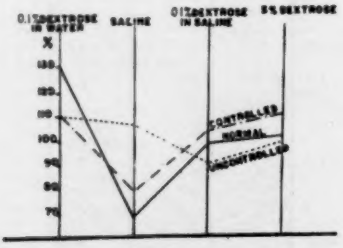

Chart 4.—Comparison of the absorption times of intracutaneous injections of solutions of dextrose and sodium chloride for persons with uncontrolled diabetes, persons with controlled diabetes and for nondiabetic subjects.

time. The lines connecting the vertical columns, therefore, indicate the values for a series of tests made at different times.

The total time for absorption of all solutions (table 1) was shortest for patients with uncontrolled diabetes and longest for normal subjects,

with patients with controlled diabetes occupying an intermediate position. Although the range of variation was rather broad for all three groups (charts 1, 2 and 3), the tendency for more of the series of readings to cluster around lower levels of absorption time was apparent for the patients with uncontrolled diabetes. It was observed (table 1) that for the last-named subjects absorption of the physiologic solution of sodium chloride and of 0.1 per cent solution of dextrose in water took the longest time (20.4 and 19.7 minutes respectively) and that of 5 per cent solution of dextrose and 0.1 per cent dextrose in physiologic saline solution required less time.

In chart 1 it may be observed that while in a number of tests the 0.1 per cent solution of dextrose in water was absorbed at a more rapid rate than was the physiologic solution of sodium chloride, in others the rate was the same or greater. The tendency for the lines to swing downward (shorter time) to the absorption level of 0.1 per cent dextrose

TABLE 1.—*Average Absorption Time*

Condition of Subject	0.1% Dextrose in Water	0.85% Solution Sodium Chloride	0.1% Dextrose in 0.85% Sodium Chloride	5% Dextrose in Water	Total Time, Minutes
Uncontrolled diabetes...	20.40	19.70	16.5	16.5	73
Controlled diabetes.....	22.5	16	21.5	22.4	82.4
No diabetes.....	25.3	18	26.0	27.3	106.6

in saline solution was clearly apparent. In case of the 5 per cent dextrose solution some of the lines swing down, some are parallel and others turn upward.

In the subjects with controlled diabetes the physiologic solution of sodium chloride required the shortest time for absorption, the 5 per cent and the 0.1 per cent solutions of dextrose in water the longest time and the 0.1 per cent of dextrose in physiologic solution of sodium chloride slightly less time. In chart 2 the altered status may be observed by the sharp swing downward of the greater number of the lines from the absorption level of 0.1 per cent solution of dextrose in water to that of physiologic solution of sodium chloride and then the definite upward swing (longer time) to the level of 0.1 per cent dextrose in physiologic solution of sodium chloride. Finally, most of the lines are either parallel or swing upward to reach the level for 5 per cent solution of dextrose, with some turning downward.

In the normal subjects (chart 3) the absorption tendencies of the solutions show the most defined pattern. Although among these subjects on the whole the solutions required a longer time for absorption than they did among patients with controlled diabetes, the close resemblance between the absorption patterns of the two types of subjects is apparent.

It was observed for patients whose diabetes was either under control or "out of control," as well as for the normal subjects, that considerable variations in the readings were obtained from time to time. In a small group which was observed daily for a week similar results were obtained. However, when the percentile ratio between the time of absorption of each solution and the average time for the series of solutions obtained on that day was taken, most of the differences between the series of readings taken on different days were eliminated. Therefore, while the rate of absorption of the various solutions varied markedly from day to day, the ratio of the time of absorption of each of the solutions to the average time for the series for that day remained fairly constant. To summarize the data obtained in terms of a percentile ratio between the average time of absorption for each of the solutions and the average time for the series for each of the three groups of subjects, chart 4 was

TABLE 2.—*Ratio of Rate of Absorption of Various Solutions to Rate of Absorption of Physiologic Solution of Sodium Chloride*

	Solution			
Condition of Subject	0.1% Dextrose in Water	0.85% Solution of Sodium Chloride	0.1% Dextrose in 0.85% Solution of Sodium Chloride	5% Dextrose
Uncontrolled diabetes	1.04	1.00	0.84	0.94
Controlled diabetes	1.41	1.00	1.34	1.40
No diabetes	1.99	1.00	1.47	1.54

drawn. It may be seen that the rate for the groups with controlled diabetes approaches that for the normal subjects.

Because comparison of absorption time of the saline solution with that of the various other solutions gave the most striking differences and because the saline solution represents an ionic solution and the others molecular solutions, all the other solutions employed were compared with it. It may be seen from table 2 that the ratio of the other solutions to the physiologic solution of sodium chloride tends to approach normal in the persons with controlled diabetes and differs more greatly in persons with uncontrolled diabetes. In the latter the values for the 0.1 per cent solution of dextrose in saline solution and for the 5 per cent solution of dextrose are less than those for the saline solution. In the persons with controlled diabetes the ratios for the 0.1 per cent solution of dextrose in water and the 5 per cent dextrose are definitely the highest, with the value for 0.1 per cent solution of dextrose in saline solution occupying an intermediate position. Among the normal subjects, the ratio for 0.1 per cent solution of dextrose in water is the

highest, with the 5 per cent solution of dextrose next and the 0.1 per cent solution of dextrose in saline solution the lowest.

A group of 10 diabetic patients was observed at frequent intervals from the time they were admitted with the diabetes out of control until the diabetes was brought under control. It was observed that it took from one to two weeks after the sugar levels of the blood and urine were brought down to normal before the absorption rates of the various solutions approached normal. The subjects with mild diabetes, the control of which was achieved and maintained by diet alone, showed the most prompt response in their absorption rates. The dextrose solutions were absorbed more rapidly than were solutions of sodium chloride before diabetic management was undertaken, while after the diabetes was brought under control the reverse was seen. On the other hand,

TABLE 3.—*Effect of Control of Diabetes on Rate of Absorption of Solutions of Dextrose and Sodium Chloride*

Condition of Subject	Solution			
	0.1% Dextrose in Water	0.85% Sodium Chloride	0.1% Dextrose in Sodium Chloride	5% Dextrose in Water
	Absorption Time			
Uncontrolled diabetes	24.5	21.2	16.2	18.2
Controlled diabetes	22	15.4	22.4	24
	Ratio of Absorption Time of Above Solutions to That of Physiologic Solution of Sodium Chloride			
Uncontrolled diabetes	1.15	1.00	0.76	0.86
Controlled diabetes	1.42	1.00	1.46	1.56

transient elevations in the level of sugar in the blood and urine were not reflected by changes in the absorption rates. The absorption rates for the same group of 10 patients, both with the diabetes out of control and with it under control, did not differ significantly from those for the larger groups of patients observed. The values obtained in the various stages of elevation of blood sugar and glycosuria were grouped together and contrasted with those obtained when the patients were sugar free and had more normal blood sugar values (table 3).

In 3 of the patients the typical changes in the ratio as the diabetes was brought under control were not observed. One patient had gangrene of the toes of one foot, the second moderately severe arteriosclerosis and the third severe diabetes.

It was found that in normal subjects (10 tests) urea was absorbed at about the the same rate as a 0.1 per cent solution of dextrose in physiologic saline solution, that is, in 25 minutes as compared with 26 minutes and that the ratio of the absorption rate to that of the saline solution was 1.41 (compare with tables 1 and 2).

For the normal persons the average absorption rate for urea was distinctly greater than that for persons with diabetes. Among the latter the absorption rate was subject to wide fluctuations, and no consistent ratio was evident whether the basis for comparison was the rates for the two states of diabetic control or the rates for the other solutions, with the exception that in persons with controlled diabetes the solution of urea was usually absorbed more slowly than was the physiologic solution of sodium chloride.

COMMENT

In the diabetic patients as a group differences in the absorption rates of the different solutions depended on whether the diabetes was controlled or uncontrolled. The total absorption time of the solutions for the patients with uncontrolled diabetes was less than for those whose diabetes was controlled. This was probably due to a measure of dehydration which occurs in persons with uncontrolled diabetes. However, this was not the only factor. The 5 per cent solution of dextrose and the 0.1 per cent dextrose in saline solution were absorbed at a slightly faster rate than was the physiologic solution of sodium chloride, while the absorption rate for the 0.1 per cent solution of dextrose in water was almost the same as that for the last-named saline solution. On the other hand, among patients with controlled diabetes the dextrose solutions were absorbed at a definitely slower rate than was the saline solution.

In any subject repeated testing may reveal wide fluctuations in absorption time of the solutions; however, the relation of the absorption time of one solution to that of another at the time of testing revealed a far greater consistency than did the rate of absorption of each solution from test to test. For example, in a person with controlled diabetes if the saline solution was absorbed rapidly at one test, the other solutions were also absorbed at a relatively rapid rate; on the other hand, if in the same patient with the diabetes still under control the saline solution was absorbed at a slower rate, the other solutions were also absorbed at a relatively slower rate and the ratio between the solutions was not appreciably changed. The fluctuations from test to test for a given person may be due to daily variations in the state of hydration.

It was evident that differences in osmotic pressure and hydration could not explain adequately all of the changes observed. For persons with controlled diabetes the relation between the rates of absorption of various solutions was similar to that evident for normal subjects and differed from that for persons with uncontrolled diabetes. This difference may, to a certain extent, be explained by the assumption of differences in permeability.

The most consistent differences were obtained with the physiologic solution of sodium chloride, as compared with the isotonic solution of dextrose. The ratio between the two (dextrose/saline solutions) for the patients with uncontrolled diabetes was 0.94; for those with controlled diabetes it was 1.40, and for the normal subjects it was 1.54. The isotonic solution of urea gave results that were subject to wider fluctuations than those obtained with the other solutions, although among the normal subjects and the patients with controlled diabetes the absorption rates were as a rule slower than those noted with the saline solution, while the differences were definitely smaller than those between the isotonic solution of dextrose and the saline solution.

The results obtained with the 0.1 per cent solution of dextrose in water and the physiologic solution of sodium chloride confirm the findings of Seelig [1] with regard to the rate of absorption by persons with uncontrolled diabetes and by nondiabetic subjects.

SUMMARY

For 3 groups, persons with uncontrolled diabetes, persons with controlled diabetes and nondiabetic subjects, the absorption rates of intracutaneous injections of physiologic solution of sodium chloride, solutions of dextrose of various concentrations and a solution of urea were studied.

Definite differences were observed between the ratio of the absorption time of various solutions of dextrose to the absorption time of saline solution for persons with uncontrolled diabetes and the ratio for persons with controlled diabetes, throughout a relatively wide range of fluctuations in the actual absorption times.

The ratio of the absorption time of the various solutions of dextrose to that of the saline solution for the persons with controlled diabetes was similar to the ratio for the normal subjects but differed from that for the persons with uncontrolled diabetes.

PROLONGED SURVIVAL AFTER PERFORATION OF THE INFARCTED INTERVENTRICULAR SEPTUM IN CORONARY ARTERIAL DISEASE

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NEW YORK

In 1934 Sager [1] reviewed the literature on perforation of the infarcted interventricular septum in coronary thrombosis and reported a case of his own in which the diagnosis was made ante mortem. The reader is referred to his paper for an excellent summary of all previously reported cases of this condition and for criteria for its diagnosis during life. In most cases the occurrence of septal perforation in the course of coronary occlusion is signalized by the sudden appearance of a forceful thrill and murmur shortly after infarction. As in congenital septal defect, the smaller the aperture the louder the murmur. Larger septal defects may be associated with a diastolic murmur as well.

Although in all the cases reviewed by Sager the patients died within ten days after the occurrence of perforation, he predicted that an occasional instance of recovery might be found in which the infarct had undergone repair with scar tissue and in which perforation had persisted. Since then Huber [2] has reported the case of a patient surviving sixteen days in whose heart organization of the edges of the defect had already begun. A patient whose case Mahrburg [3] reported lived four weeks, and at autopsy a fibrous bulge containing four small defects was found in the septum. Gross and Schwartz [4] described a circular septal defect, several centimeters in diameter, occurring in a patient who died fourteen months after the onset of chronic cardiac failure. In the case reported by Stanley [5] the diagnosis was made clinically, and the patient eventually died of heart failure with hemiplegia five months after the onset.

From the laboratory and medical service of St. Peter's Hospital, New Brunswick, N. J.

1. Sager, R. V.: Coronary Thrombosis: Perforation of the Infarcted Interventricular Septum, Arch. Int. Med. **53**:140 (Jan.) 1934.

2. Huber, H.: Ueber erworbene Defekte der Herzkammerscheidewand, Ztschr. f. Kreislaufforsch. **27**:825, 1935.

3. Mahrburg, S.: Durchlöcherung der Herzkammerscheidewand mit chronischem Verlauf, Frankfurt. Ztschr. f. Path. **47**:552, 1935.

4. Gross, H., and Schwartz, S. P.: A Case of Acquired Interventricular Septal Defect Associated with Long-Standing Congestive Heart Failure, Am. Heart J. **11**:626, 1936.

5. Stanley, D. F.: Acquired Interventricular Septum Defect: Report of a Case, Am. Heart J. **14**:240, 1937.

REPORT OF A CASE

History.—C. H., a chemical operator 57 years old, was admitted to St. Peter's Hospital Jan. 11, 1939. He had been well until one month before admission, when he had an attack of severe precordial pain which lasted throughout the night. After that he had constant dull pain in both loins and a severe dry cough. Two weeks after the onset he became short of breath on slight exertion and began to have pain in the right upper quadrant of the abdomen.

Physical Examination.—The patient was well developed and well nourished. He appeared weak, dyspneic, pallid and slightly cyanotic. The veins of his neck were distended and pulsating, and he was unable to lie flat. The heart was greatly enlarged to the left and downward. The heart sounds were poor, and a loud systolic murmur and a diastolic murmur were heard over the apex. A palpable thrill was also felt over the apex. These murmurs were not transmitted to the base. The second aortic sound was faint, and the second pulmonic sound was accentuated. The pulse rate was 94 beats per minute; the pulse was weak,

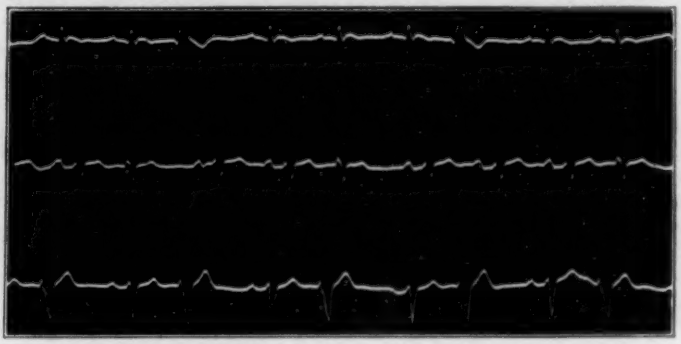

Fig. 1.—Electrocardiogram taken one month after the onset of symptoms.

and the rhythm was irregular as a result of frequent premature beats. The blood pressure was 118 systolic and 70 diastolic. Moist rales were heard at the base of the left lung posteriorly, and signs of pleural effusion were noted at the base of the right lung. The liver was markedly enlarged and tender. No edema or ascites was detected.

Laboratory Examination.—Examination of the blood yielded the following information: hemoglobin concentration, (Sahli) 81 per cent; red cells, 4,200,000 per cubic millimeter; white cells, 5,800 per cubic millimeter, with 66 per cent polymorphonuclear leukocytes; Wassermann reaction, negative; urea nitrogen, 8.5 mg. per hundred cubic centimeters, and sugar, 85 mg. per hundred cubic centimeters. The urine was acid and had a specific gravity of 1.028; albumin was present in a moderate trace, but there was no sugar or acetone. Microscopically, a few white cells were seen. Roentgenologic examination of the chest revealed a markedly enlarged heart of aortic type and a pleural effusion on the right side.

Electrocardiogram.—The electrocardiogram (fig. 1) showed a regular sinus rhythm interrupted by many ventricular premature beats. The rate was about 75 beats per minute. The P waves were wide and notched, of the type associated

with auricular enlargement. The auriculoventricular conduction time, i. e., the PR interval, measured about two-tenths second, the upper limit of normal. The QRS complexes were wide, notched and slurred, with left axis deviation, and the RST transitions in leads I and II were slightly elevated.

Clinical Diagnosis.—The sudden onset of symptoms followed by rapid cardiac decompensation suggested coronary arterial occlusion. The wide, notched and slurred QRS complexes in the electrocardiogram indicated intraventricular block, as is seen in cases of damage to the septum, and the elevation of the RS-T segment indicated recent myocardial damage.[6] The large heart of aortic type, the loud systolic murmur, the precordial thrill, the faint second aortic sound and the slightly low blood pressure also suggested the presence of aortic stenosis as a cause of the failure of both ventricles. The possibility of ventricular septal defect was not considered.

Course.—The patient lived twelve weeks after admission to the hospital. In the course of this time the evidences of failure of the right side of the heart increased, despite treatment with digitalis and mercurial diuretics. Sacral and scrotal edema appeared, and repeated thoracentesis was required because of the rapid reaccumulation of fluid in the right pleural cavity. A roentgenologic examination of the chest after withdrawal of fluid revealed shrinkage and dense consolidation of the lower third of the right lung. The venous pressure measured by the direct method was 23.5 cm., rising to over 26 cm. on pressure over the right upper quadrant. The swelling of the liver became enormous, and slight icterus appeared. On March 3 moderate renal impairment was indicated by the rise of urea nitrogen to 27.3 mg. per hundred cubic centimeters of blood and by the excretion of only 12 per cent of injected phenolsulfonphthalein in two hours. In view of the normal concentrating ability of the kidney, these findings were attributed to chronic passive congestion of the kidneys. The intractable tendency to edema and effusion was attributed to the combination of heart failure, renal insufficiency and hypoproteinemia, the last being ascribed to undernutrition and possibly hepatic insufficiency. The proteins of the plasma were found to be 4.6 Gm. per hundred cubic centimeters, with a globulin deficiency (albumin 3.5 Gm., globulin 1.1 Gm.). The patient's temperature remained normal throughout most of his stay in the hospital; in the first two weeks his cardiac rate ranged between 40 and 48 and thereafter between 72 and 82 per minute. His blood pressure did not change significantly. Despite his poor condition, the harsh systolic murmur at the apex was distinct at all times and the pulmonic second sound remained accentuated. He died on April 12, 1939, approximately four months after the onset of his cardiac symptoms.

Postmortem Examination.—The anatomic diagnoses were as follows: coronary atherosclerosis, with complete occlusion of the left anterior descending branch and moderate narrowing of the right coronary artery; healed myomalacia, with extensive fibrosis of the left ventricle and the interventricular septum; large aneurysm of the left ventricle; double perforation of the interventricular septum in the area of previous infarction; localized endocardial sclerosis of the right ventricle opposite the perforation; localized pericardial adhesion; hypertrophy and dilatation of the right ventricle; anasarca, with enormous right hydrothorax; complete compression atelectasis of the entire right lung, with chronic serofibrinous pleuritis; compensatory emphysema of the left lung; chronic passive congestion of the liver (marked), spleen, kidneys, gastrointestinal tract and lungs; slight icterus; acute gastric dilatation, and anemic infarction of the right kidney.

6. The electrocardiogram reported here was interpreted by Dr. Arthur Master.

Examination of the Heart.—The heart weighed about 400 Gm. The pericardial surfaces were smooth, except for an area of dense fibrous adhesion about 4 cm. wide overlying the anterior interventricular groove in its middle portion. The anterior wall of the left ventricle beneath this point was extremely thin and flabby and was stretched into an aneurysmal pocket. When the left ventricle was opened (fig. 2) the aneurysm was seen to be much larger than was apparent externally. Its size approximated that of a small orange. It was formed in part by the anterior wall of the left ventricle and in part by the adjacent interventricular septum. Its inner surface was composed of tough, gristly, pearly white fibrous tissue overlaid by an area of adherent mural thrombus. The latter, which was grayish red, projected considerably into the lumen of the aneurysm and measured about 4 cm. in width. The greatest thickness of the wall of the aneurysm was less than 5 mm. It involved about five sixths of the interventricular septum

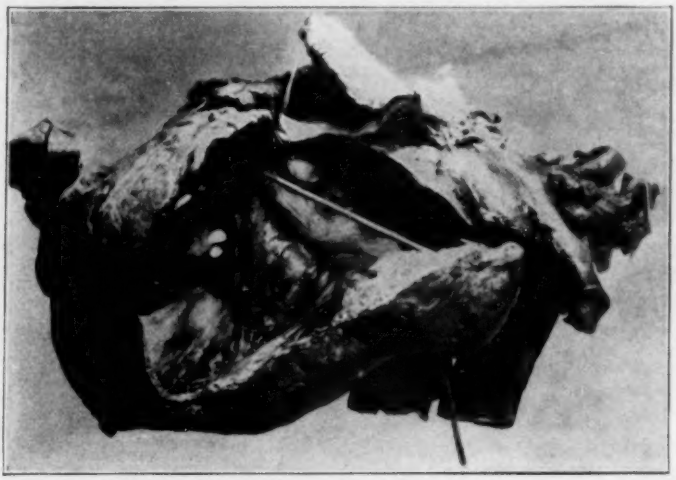

Fig. 2.—Left ventricle opened to show the double perforation of the septum and the aneurysmal dilatation and thinning of the anterior wall. Note also the wide scarring of the septum, overlaid in part by a mural thrombus. A strip of adherent pericardium is visible on the anterior surface of the ventricular aneurysm.

and was thinnest at its upper mesial border, where the muscle substance was replaced by white scar tissue 1 mm. thick. Here two ovoid perforations were seen, separated by a bridge of firm scar tissue 2 mm. wide. The lower perforation was 4 mm., the upper 5 mm., in greatest diameter. Their circumferences were thin and perfectly smooth and did not yield to stretching. In addition to the aneurysm, the left ventricle presented considerable dilatation and some hypertrophy, especially in its posterolateral portion and in the anterior papillary muscle.

Section of the myocardium showed patchy fibrosis.

The right ventricle was considerably dilated and hypertrophied. The right ventricular surface of the septum presented only a moderate bulge, which was most pronounced in the region of the perforations where the septum had become

entirely replaced by scar tissue. The latter formed an irregular, pearly white streak extending a few centimeters above and below the perforations (fig. 3). The remainder of the right ventricular endocardium was of usual appearance, except for a well defined round patch of whitish endocardial thickening on the anterior wall. This area measured about 2 cm. in width and was situated in the outflow tract of the right ventricle immediately opposite the septal perforation. On section the sclerosis was found to be confined to the endocardial layer. The anterior descending branch of the left coronary artery was markedly narrowed by calcified atheroma beginning 0.5 cm. below its origin, and in several places it was totally occluded. A small bulging plaque of soft atheroma in the intima of the right coronary artery about 3 cm. from its origin caused moderate narrowing of its lumen. The remaining coronary arterial branches showed some atheroma but no significant narrowing. The coronary ostiums were patent. The endocardium of the valves was free of significant change.

Fig. 3.—Interior of the right ventricle showing septal perforations. Note the hypertrophy of the wall of the right ventricle opposite the septum and the circumscribed area of white endocardial sclerosis (incised post mortem).

Lungs.—The right pleural cavity contained about 2,500 cc. of yellowish, slightly turbid fluid. The right lung was completely collapsed in a uniform manner which preserved its shape but reduced it to about one-third its normal size. It was peculiarly firm and rubbery, and its surface was thinly overlaid with fibrinous exudate, which had a reticulated appearance. On section the lung tissue appeared completely airless and totally consolidated. The bronchi were correspondingly narrowed. The left lung was somewhat emphysematous, and on section appeared congested and mottled, with a few small areas of slight pneumonic infiltration. In contrast to the right lung, the left lung cut with great ease. The tracheobronchial nodes were small and anthracotic.

Microscopically, sections of the right lung showed marked alveolar atelectasis and compression of bronchioles. The capillaries were dilated and tortuous, and the alveolar epithelium was swollen and desquamated. The veins were distended with blood, and the interlobular and peribronchial septums and subpleural connective tissue were edematous and moderately infiltrated with leukocytes, chiefly

mononuclear in type. The arteries and arterioles were slightly narrowed by fibrous intimal hyperplasia and medial hypertrophy. Dense masses of hyalinized fibrin were deposited on the outer layer of the pleura. Sections of the left lung showed mild uniform hyperinflation of the alveoli and marked capillary congestion, with recent patchy hemorrhage. Veins were distended with blood, and slight fibrous thickening was apparent in the media. Patchy slight fibrinopurulent exudate was present in the alveoli.

COMMENT

The congenital variety of uncomplicated defect of the interventricular septum is of little clinical significance in most cases. Acquired septal defect is probably always of serious import, depending on the nature of the underlying disease (septal infarction, septal ulceration [7]) and on the sudden imposition of unusual strain late in life on an aging right ventricle. In most cases of septal defect which results from coronary closure death occurs within the first few days from the acute heart failure and circulatory shock of extensive myocardial infarction. In the rare case of survival beyond the critical phase of infarction death is almost inevitable within a few months as a result of right ventricular failure. Although only 3 other cases are on record in which the patient lived one month or longer after septal rupture, congestive heart failure was pronounced in all of them, as well as in the case just described. One is impressed in these cases with the unyielding character of the right ventricular failure that occurred in spite of persistent efforts at treatment. On the other hand, left ventricular failure was not marked, and, as is often noted in cases of other types of heart failure, it was mitigated to a great extent by the insufficiency of the right ventricle.[8]

The mechanism of heart failure in these 4 cases of septal perforation can be explained in terms of at least three components: the leak from the left to the right ventricle, the fibrous replacement of the septal myocardium and the permanent injury to part of the left ventricle. Apparently the burden in these cases was borne chiefly by the right ventricle. Clinically anasarca and hepatic engorgement were the dominant features; the pulmonic second sound was greatly accentuated in 2 cases in which it was mentioned, and autopsy disclosed considerable hypertrophy and dilatation of the right ventricle. In the case herein reported the venous pressure was recorded as 23.5 cm. (direct method), and at autopsy a telltale plaque of endocardial sclerosis opposite the septal fistula indicated the force with which the jet of blood from the left ventricle struck the opposite wall of the right ventricle.[7] The small area and uniform appearance of this plaque are of interest as proof of the

7. Saphir, O.: Anatomic Evidence of Functional Disorders of the Heart, Arch. Path. **16**:315 (Sept.) 1933.

8. Fishberg, A. M.: Heart Failure, ed. 2, Philadelphia, Lea & Febiger, 1940, p. 449.

constancy of direction of the jet and as a minor confirmation of Moschcowitz' thesis that vascular sclerosis is determined by intravascular tension.[9]

Right ventricular failure subsequent to coronary occlusion is not to be regarded, however, as necessarily indicative of septal perforation. In the majority of cases it is the result of failure on the left side and is commonly explained by backward pressure through the pulmonary circulation, by recurrent pulmonary emboli and by other factors. Among the last should be mentioned the excessive intrusion within the right ventricular cavity of the bulging convexity of the interventricular septum associated with marked concentric hypertrophy of the left ventricle (Bernheim syndrome).[10] Another cause of septal bulging, myomalacia with replacement fibrosis, was seen in the case reported here, in which most of the septum and part of the anterior wall of the left ventricle formed a large aneurysmal sac.

In many instances of coronary disease with right-sided failure the aforementioned mechanisms seem inadequate to explain the degree of failure. The relative immunity of the right ventricle to coronary infarction adds to the difficulty of explanation. Perhaps this difficulty is the result of the current tendency to make sharp distinctions between left ventricular and right ventricular function, as exemplified in special forms of heart failure. While such distinctions are of great clinical usefulness, they tend to perpetuate the old concept of two simultaneously but independently acting ventricles. The important anatomic studies of MacCallum,[11] Mall,[12] the Robbs [13] and others have opened new avenues of research into the physiology of the ventricular musculature. Of six well defined muscle tracts of the ventricles, only one, the deep bulbospiral muscle, lies wholly within the left ventricle; the other five muscles contribute through their origins and insertions to the formation of both ventricles. The superficial sinospiral and the superficial bulbospiral muscle arise from the right and the left atrioventricular rings, respectively, and wind downward and across the anterior and the posterior

9. Moschcowitz, E.: The Cause of Arteriosclerosis, Am. J. M. Sc. **178**:244, 1929.

10. Fishberg,[8] p. 447.

11. MacCallum, J. B.: On the Muscular Architecture and Growth of the Ventricles of the Heart, in Contributions to the Science of Medicine, Dedicated by His Pupils to William Henry Welch on the Twenty-Fifth Anniversary of His Doctorate, Baltimore, Johns Hopkins Press, 1900, p. 307.

12. Mall, cited by Robb and Robb.[13c]

13. (*a*) Robb, J. S.; Hiss, F., and Robb, R. C.: Localization of Cardiac Infarcts According to Component Ventricular Muscles, Am. Heart J. **10**:287, 1933. (*b*) Robb, J. S.: The Structure of the Mammalian Ventricle, M. Woman's J. **41**:65, 1934. (*c*) Robb, J. S., and Robb, R. C.: Abnormal Distribution of the Superficial Muscle Bundles in the Human Heart, Am. Heart J. **15**:597, 1938.

interventricular groove toward the apex, where they penetrate deeply to form the papillary muscles of the mitral valve. The deep sinospiral muscle, which arises from nearly the entire circumference of the left atrioventricular ring, curves downward over the lateral and posterior wall of the left ventricle, where it forms the rounded, fleshy lower border (margo obtusus), and splits at the posterior interventricular groove to enclose the cavity of the right ventricle, comprising 75 per cent of its substance normally. The scroll muscle arises deep within the base of the right ventricle, completely encircles its upper portion in a clockwise course and thence passes forward through the septum to reach the superficial layers of the left ventricle anteriorly, where it fuses with the fibers of the superficial muscles. The longitudinal interventricular muscle arises from both atrioventricular rings and the aortic septum and courses forward and downward through the septum to emerge anteriorly, where it fuses with the superficial sinospiral muscle above the apex. From the foregoing descriptions it is apparent that the superficial sinospiral and the superficial bulbospiral muscle encircle both ventricles externally and that the deep sinospiral muscle and the scroll muscle encircle both ventricles more deeply. The septum is contributed to by the deep sinospiral muscle, the scroll muscle and the longitudinal interventricular muscle. Experimental injury of selected muscle tracts produces serious functional impairment of the ventricles in the case of the deep muscles and relatively insignificant impairment in the case of the superficial muscles.[13a]

It remains for future workers to determine the extent to which these separate muscle tracts act as functional units. Can necrosis through infarction of an individual muscle at one point of its course cause serious disruption of its function as an entire unit? Certain intimations of this possibility are observed clinically, for instance in those cases of predominant right ventricular failure that results from extensive infarction of the left ventricle not including the septum in which the degree of pulmonary congestion is not especially outstanding. Such cases, for want of a better explanation, have been considered by some as examples of "forward failure." As an alternative hypothesis, the suggestion is offered that in such cases a remote injury, e. g., one in the left ventricle, may communicate its effects to the right ventricle through individual muscle tracts which are continuous in both ventricles. The greatest threat to normal function of the right ventricle has been shown to lie in injury to the deep sinospiral muscle, which contributes about three fourths of the muscle substance of the right ventricle. This muscle, moreover, is vulnerable to injury over a large area within the lateral and posterior wall of the left ventricle before it enters into the formation of the right ventricle and is often involved in infarction of the posterior and lateral wall of the left ventricle. In cases of infarction of the septum

a number of important fiber tracts may be caught in a relatively small area of injury, with the result that either the left or the right or both ventricles may suffer. On the other hand, according to the same hypothesis, the septum itself may suffer as a result of infarction of one of its constituent muscles at some point within the left ventricle.

It is rather surprising that the role of the interventricular septum in cardiovascular dynamics has not been stressed to the degree that it deserves. The case recorded here, in which right-sided failure was outstanding, focuses attention on the septum as a truly important element in this problem. The functions which are peculiar to the septum are not easily understood, unless by analogy. The anatomic justification for ascribing an active and independent function to the septum is found in the existence of such muscles as the scroll muscle and the longitudinal interventricular muscle, previously described. In both these the fibers are directed in a way to suggest that their chief activity consists in shortening the septum along each major axis during systole. Its effect is probably both to aid in the systolic contraction of the heart as a whole and to preserve the normal differential in intracardiac pressures of the left and the right ventricle during systole and diastole. Septal failure through myofibrosis or perforation permits the heart to revert to a condition approaching that of the cor triloculare, in which blood is propelled by a common ventricle. In that case the burden is transferred to those layers of the heart muscle which are common to both ventricles. The task of maintaining the systolic and diastolic tension in the systemic arteries must then be shared in unusually great part by the right ventricle. When this extra burden proves beyond its powers decompensation is largely, if not entirely, manifested as right-sided failure.

SUMMARY

Rupture of the left ventricle after infarction is immediately fatal unless the area of softening is situated in the interventricular septum. In the latter case death may be delayed several days, and then occur as a result primarily of the severe shock and heart failure resulting from coronary occlusion. Prolonged survival is rare and is characterized by intractable right ventricular failure and the presence of the harsh systolic murmur of interventricular septal defect.

The interventricular septum considered as a functional entity is of particular significance, both as a component of deep muscle tracts common to both ventricles and as an agency for protecting the right ventricle by preserving the differential in pressure between the two ventricles.

PRIMARY PORTAL PHLEBOSCLEROSIS

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Although phlebosclerosis of the portal system is recognized as a primary entity, its definition is obscure and its pathogenesis and etiology require further investigation. Since its occurrence has been adequately established,[1] it should be more carefully sought for at autopsy. It is the purpose of this paper to indicate how it may be clinically identified more frequently. It is also proposed to employ henceforth the name "primary portal phlebosclerosis" for clarification and uniformity.

Up to 1928,[2] 29 cases were reported in children, but few in adults. The exact number is difficult to ascertain in view of the existing confusion. In many of these cases the condition appeared to resemble Banti's syndrome, as it did in my case. However, on further study or at autopsy, the question of some primary obstruction of the portal circulation, with or without coexisting thrombosis or sclerosis of either the splenic or the portal vein or of both, arises. Wilson and Lederer [2] presented the case of a boy aged 16 months. Haenelt [3] added another case and mentioned 8 cases in the literature in which the condition was designated as Banti's syndrome but at autopsy proved to be either portal

From the service of Dr. C. H. Greene, Kings County Hospital, and the Long Island College of Medicine Division, J. Hamilton Crawford, Director.

1. (*a*) Spiegelberg, H.: Verkalkung der Wandungen der thrombotischen Pfortader, Virchows Arch. f. path. Anat. **142**:547, 1895. (*b*) Borrmann: Beitrage zur Thrombose der Pfortaderstammes, Deutsches Arch. f. klin. Med. **59**:283, 1897. (*c*) Welch, W. H.: Thrombosis, in Allbutt, T. C.: System of Medicine, New York, Macmillan & Company, 1899, vol. 7, p. 155. (*d*) Buday, K.: Ueber die Sklerose der Pfortader, Centralbl. f. allg. Path. u. path. Anat. **5**:161, 1903. (*e*) Hart, C.: Ueber die kavernöse Umwandlung der Pfortader, Berl. klin. Wchnschr. **50**:2231, 1913. (*f*) Winkler, H.: Ueber primäre Pfortaderthrombose bei Pfortadersklerose und bei chronischen Milztumor, Ztschr. f. Path. **17**:377, 1915. (*g*) Gruber, G. B.: Beiträge zur Pathologie der dauernden Pfortaderverstopfung, Deutsches Arch. f. klin. Med. **122**:319, 1917.

2. Wilson, S. J., and Lederer, M.: Splenomegaly Portal Phlebosclerosis, Am. J. Dis. Child. **38**:1231 (Dec.) 1929.

3. Haenelt, M.: Beitrag zur Frage der Sklerose im Pfortadergebiet, Med. Klin. **24**:622 (April 20) 1928.

or splenic phlebosclerosis, as described microscopically by Brüning and Schwalbe.[4]

The exact point of obstruction may occur anywhere in the portal system. In the case reported by Wilson and Lederer [2] the constriction occurred in the proximal portion of the portal vein. Galloway [5] found the point of obstruction at the junction of the splenic and the mesenteric vein. In my case, both the portal vein and its splenic branch were involved.

REPORT OF A CASE

R. L., an Italian woman aged 21, entered Kings County Hospital with a history of gastric hemorrhage, with loss of 1 quart (946 cc.) of blood, seven years before, at the age of 14. The following year she had had three hematemeses in twenty-four hours but no other complaints. A diagnosis of Banti's disease was made, and splenectomy was performed at that time. However, hemorrhages persisted and were severe, amounting to several pints each time. A similar attack was the occasion for her entrance to the hospital. Weakness was rapidly progressive. Prior to the onset seven years before she had been in good health. She had suffered from influenza seven years previously, scarlatina and diphtheria at the age of 1 year, but had had no trauma, infections or operations. She seldom smoked, occasionally took alcohol and was a moderate coffee drinker. The father had died at the age of 22 of pneumonia, and the mother had disappeared.

The patient was well developed and well nourished and appeared acutely ill. There was evidence of air hunger. The edge of the liver was firm and palpable at the costal margin. There was no fluid or mass.

Laboratory studies revealed severe secondary anemia, with normal white cell and differential counts. The results of urinalysis were essentially normal. The blood contained 100 mg. of sugar, 1.6 mg. of creatinine, 75 mg. of urea, 3.7 mg. of albumin and 2.0 mg. of globulin per hundred cubic centimeters; the albumin-globulin ratio was 1.8; the spinal fluid was normal, and the Wassermann reaction of the blood was negative. Findings seven years previously had revealed normal erythrocyte fragility, a negative Widal reaction, sterile blood cultures, severe secondary anemia, an icteric index of 4.5 and normal roentgenograms of the gastro-intestinal tract and the chest.

A diagnosis of Banti's disease, with rupture of an esophageal varix, was made. About two and one-half weeks after admission the patient had another hemorrhage. She went into shock and was given a transfusion, with rapid improvement. The following day an operation was performed. Two large veins on the diaphragm, crossing toward the esophagus and nearly 0.5 cm. in diameter, were ligated. Two cubic centimeters of sodium morrhuate was injected into a large vein on the lesser curvature of the stomach. After the operation a temperature of 103 F. developed. The patient's course of illness was rapidly downhill, and she died three days after the operation.

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4. Brüning, H., and Schwalbe, E.: Handbuch der allgemeinen Pathologie und der pathologischen Anatomie des Kindesalters, Munich, J. F. Bergmann, 1924, vol. 2, p. 1225.

5. Galloway, J.: Splenomegaly with Anemia and Hemorrhages, Brit. J. Child. Dis. **13**:64, 1916.

The spleen, removed at the Metropolitan Hospital seven years previously, weighed 493 Gm. It was reported to have been enlarged, congested and firm. The edge of the cut section was sharp and flat, and the pulp was purplish red. The splenic vessels were enlarged. Microscopically, there was marked perivasculitis of fibrous type, with hyperplasia of the trabeculae. The germinal centers appeared large in some places and small in others. The parenchyma was congested, but no blood pigment was present. No note was made concerning the appearance of the portal vein. A diagnosis of Banti's disease was made.

On postmortem examination, the portal vein was of uniform caliber but its internal diameter was only about half the normal, measuring 0.5 cm. It was almost completely occluded by an adherent gray thrombus, which left only an eighth of the lumen patent. The superior mesenteric vein was also markedly narrowed and presented the same appearance as the portal vein. Most of the tributaries of the superior mesenteric vein to the small and the large bowel were occluded by adherent gray thrombi. The superior and inferior hemorrhoidal veins were dilated and slightly varicosed but not thrombosed. Many of the veins about the cardiac end of the stomach were prominent, varicosed and thrombosed. The paraumbilical vein was represented by a fibrous strand. There was no caput medusae. The thoracoepigastric vein was not prominent superficially; the azygos vein was moderately dilated, and there were many varicose veins in the lower half of the esophagus, but no point of rupture was found. The left common iliac vein was completely occluded by a gray adherent thrombus, the center of which was loose and necrotic. This could be traced distally into the external iliac and femoral veins, and it extended for about 1 inch (2.5 cm.) into the proximal portion of the hypogastric vein. The inferior vena cava was smooth throughout and free of thrombi. The right common iliac vein was patent and the intima was smooth. On the upper left side the great omentum and its vessels were adherent to the parietal peritoneum covering the lateral abdominal wall. The splenic artery was markedly narrowed, and there were a few small sclerotic plaques in its intima. The coronary arteries and aorta were normal. The branches of the pulmonary artery in the lower lobe of the right lung were filled with loosely adherent, gray, soft thrombi, with the production of multiple hemorrhagic infarctions. The blood vessels of the cardiac portion of the stomach were prominent. In the jejunum there was an area of venous infarction 2 inches (5 cm.) in length which was softened and friable.

Microscopically (figs. 1, 2 and 3) the liver showed marked fatty changes replacing the liver cells, the lobular architecture being fairly well preserved. There were round cell infiltrations around proliferated bile ducts and portal canals, as well as moderate reduplication of the small bile ducts. There was also chronic adhesive perihepatitis. The portal vein was filled with early organizing thrombi, and the wall showed evidence of marked thickening due to increased fibrous connective tissue in all layers. The smooth muscle was replaced by irregularly hyalinized areas of connective tissue. There was no evidence of atheromatous change or calcification. There were marked fibrous tissue proliferation and diffuse round cell infiltration surrounding the thrombi. The internal elastic membrane was frayed, thickened and interrupted. The final anatomic diagnosis was primary phlebosclerosis of the superior mesenteric and splenic veins; multiple thromboses of the portal, superior mesenteric, left common iliac, external iliac, femoral, hypogastric and pulmonary veins, the submucosal veins of the stomach and the small intestine and the veins of the lymph nodes, and secondary anemia.

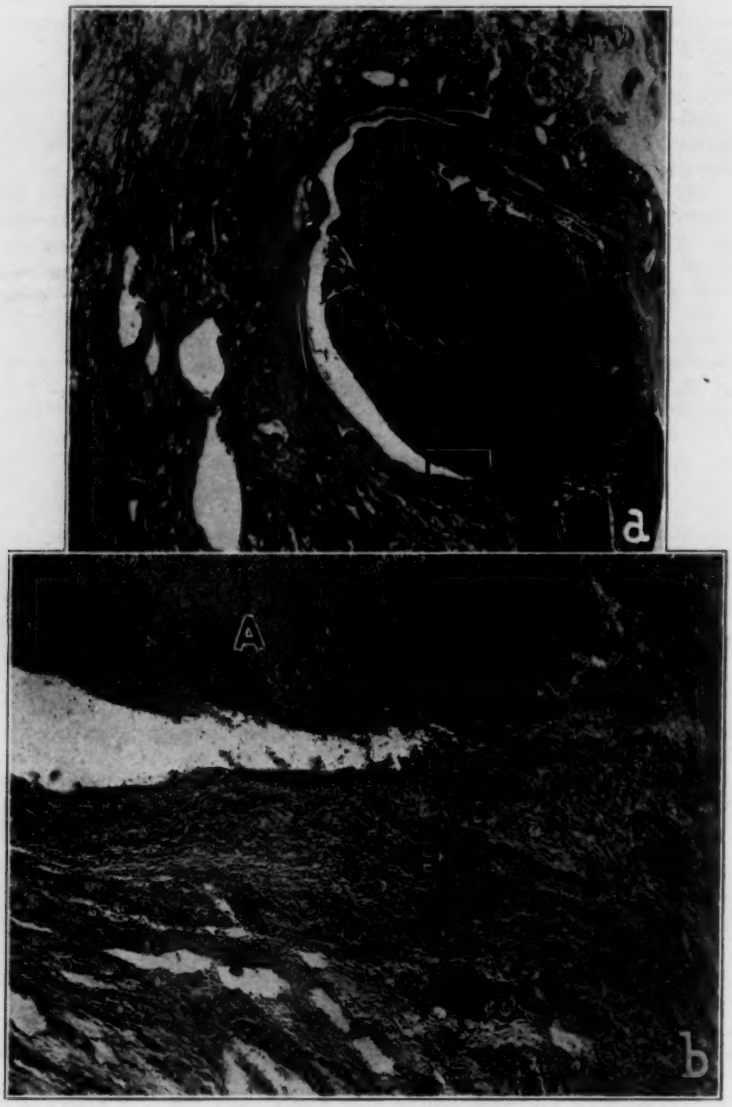

Fig. 1.—(*a*) A thickened vein and an attached thrombus (× about 10). (*b*) A greater magnification (× about 70) of the tissue in (*a*) indicated by square, the thrombus (*A*) at the point of attachment and the wall of the vein (*B*). The venous wall shows evidence of marked thickening due to fibrous connective tissue and hyalinization. The smooth muscle is replaced by irregular hyalinized areas of connective tissue. There is no evidence of calcification.

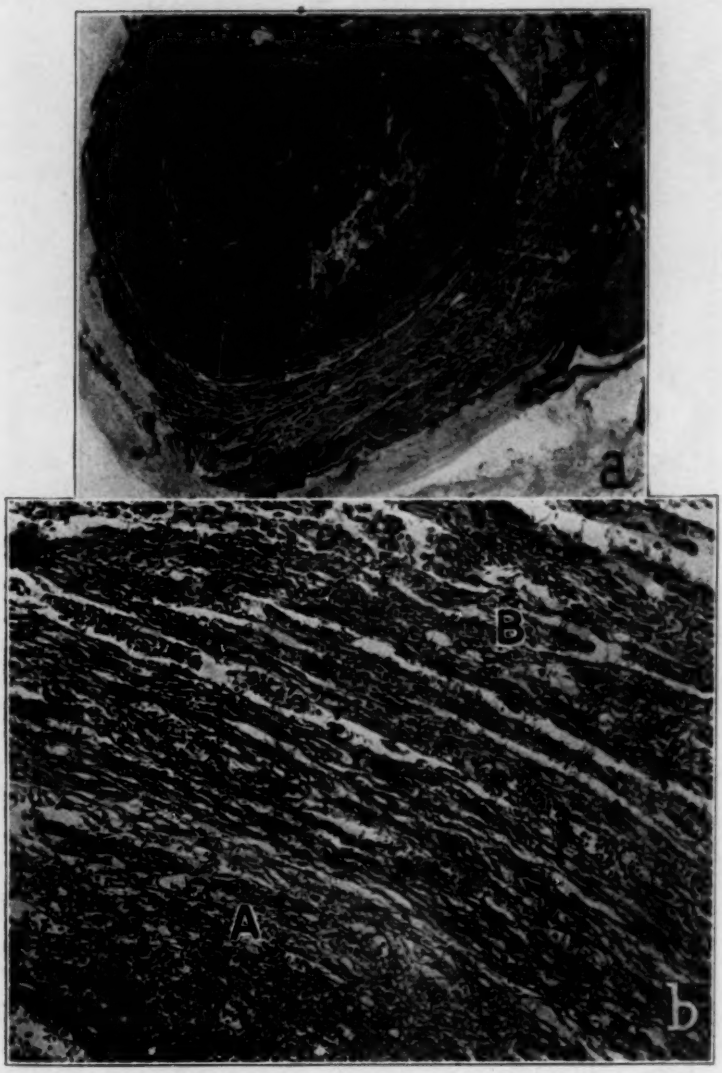

Fig. 2.—(*a*) Complete occlusion of the portal vein by an organizing thrombus (× about 10). (*b*) The attached thrombus (*A*) and the wall of the vein (*B*) more highly magnified (× about 142), showing the marked proliferation of fibrous tissue and the diffuse round cell infiltration surrounding it. The elastica is frayed, thickened and interrupted.

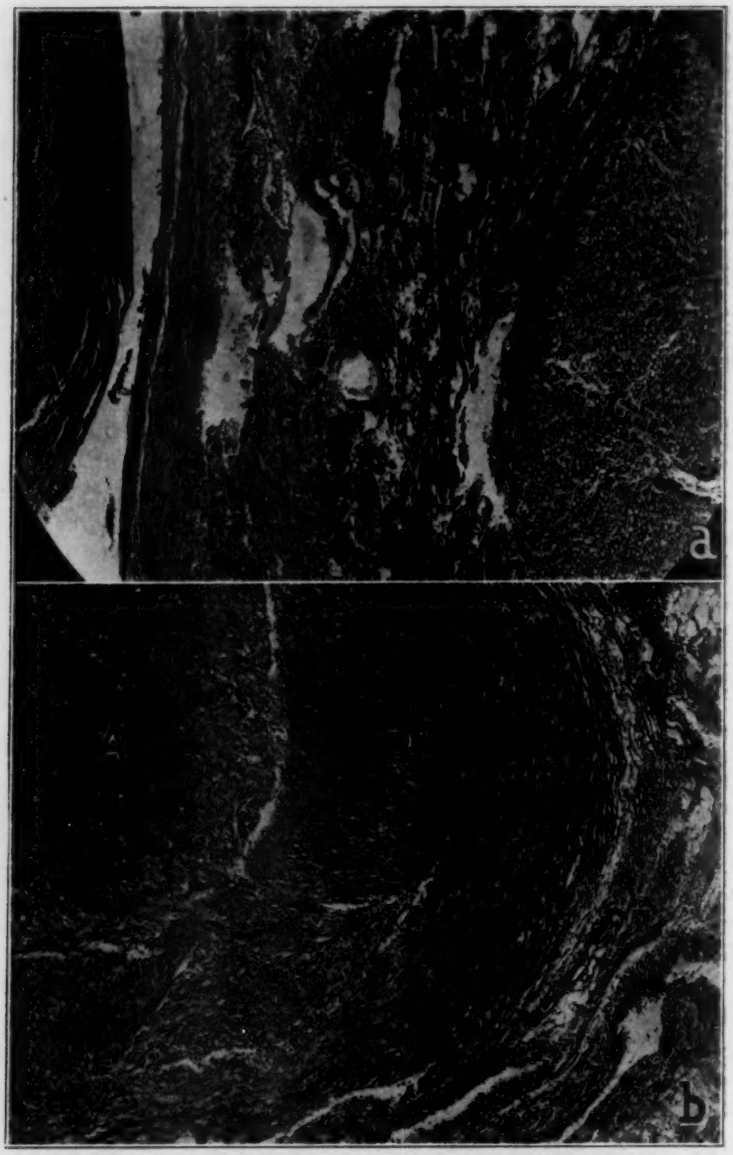

Fig. 3.—(*a*) An occluding thrombus (*A*) of the portal vein, with partial organization and disintegration. Also visible are the typical necrotic changes (*B*) and marked fatty changes of the hepatic cells (*C*), although the lobular architecture is well preserved. There is marked proliferation of the bile duct, with reduplication and round cell accumulations (× about 55). (*b*) A large organizing thrombus (*A*) adherent to the wall of the superior mesenteric vein (*B*). The latter shows the usual fibrotic thickening (× about 68).

PATHOLOGY

It has long been argued that the extreme splenomegaly of Banti's syndrome is due to primary obstructive lesions of the portal and splenic veins.[6] Nevertheless, the fact that the spleen in cases of cardiac decompensation never shows such extreme enlargement is somewhat against this view. Menon [7] by experimental operation produced the same effect as does a narrowed portal vein lumen. He found that after complete occlusion the spleen swells to three times its size, with resulting infarc-

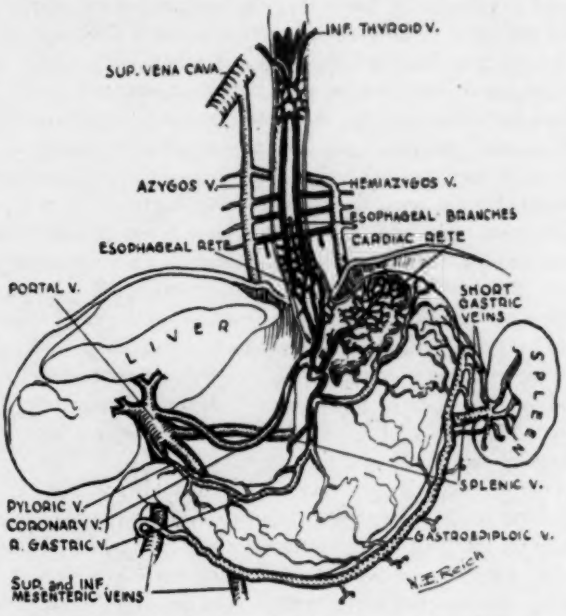

Fig. 4.—"Formation of varices in the esophagus and cardia. Note that the upper third of the stomach and esophagus has been exposed by removal of the anterior wall" (from Plotz and Reich [16]).

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6. (*a*) Dock, G., and Warthin, A. S.: A Clinical and Pathological Study of Two Cases of Splenic Anemia, with Early and Late Stages of Cirrhosis, Am. J. M. Sc. **127**:24, 1904. (*b*) Klemperer, P.: Pathologic Anatomy of Splenomegaly, Am. J. Clin. Path. **6**:99, 1936. (*c*) Warthin, A. S.: The Relation of Thrombophlebitis of the Portal and Splenic Veins to Splenic Anemia and Banti's Disease, Internat. Clin. **6**:189, 1910. (*d*) Klemperer, P.: Cavernomatous Transformation of the Portal Vein: Its Relation to Banti's Disease, Arch. Path. **6**:353 (Sept.) 1928.

7. Menon, T. B.: Venous Splenomegaly: A Study in Experimental Portal Congestion, J. Path. & Bact. **46**:357 (March) 1938.

tion. After prolonged partial obstruction, little enlargement occurs. The spleen shows dilatation of the sinuses, distention of the pulp and trabecular veins and variable atrophy of the pulp, with slight fibrillary increase. Hyperplastic reactions are absent. His experiments tend to disprove, therefore, the long-held view that Banti's syndrome is due to a blockage of the portal vein. Some other factor is essential to induce proliferative changes in the spleen. An excellent description of the gross and microscopic pathology of the splenomegaly associated with sclerosis of the portal and splenic veins has been presented by Klemperer.[8d] Thompson [8] expressed the belief that the histopathologic changes in the spleen are the same in all cases of splenomegaly. They are similar in type to the changes described by Banti and others.

According to Adami,[9] the lesion of the vein is due to a strain fibrosis. The walls become thicker; the connective tissue is hypertrophied in all layers; the media presents tears and degeneration of the elastic tissue, and the intima contains connective tissue poor in nuclei. According to Simmonds [10] there is no inflammation and the process is analogous to that in atherosclerosis. In favor of this view is the resemblance of the portal vein to an artery by reason of its muscle fibers and the absence of valves. Benda [11] expressed disagreement with this view and suggested that a compensatory thickening develops on the basis of inflammatory as well as degenerative changes. In favor of this assumption may be cited the occurrence of mesenteric thrombosis with embolization of the portal vein in cases of postoperative abdominal infection, umbilical granuloma, infections and furunculosis during infancy, with resultant involvement of the portal system.

Gruber [1g] showed the presence of congenital stenosis of the portal vein, which he attributed to the remains of some intra-abdominal pathologic condition acquired during intrauterine life. The mechanical effect of adhesions must not be overlooked. Wahlgren [12] presented 4 cases in which adhesions occurred between the spleen and the stomach and either narrowing of the vein from within or compression from without. He found the changes in the peripheral branches of the portal vein. The stenosis was followed by thrombosis and stasis.

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8. Thompson, W. P.: Pathogenesis of Banti's Disease, Ann. Int. Med. **14**:255 (Aug.) 1940.

9. Adami, J. G., in Allbut, T. C., and Rolleston, H.: System of Medicine, New York, The Macmillan Company, 1910, vol. 1, p. 799.

10. Simmonds, cited by Benda, in Aschoff, L.: Pathologische Anatomie, Leipzig, Johann Ambrosius Barth, 1921, vol. 2, p. 91.

11. Benda, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 829.

12. Wahlgren, A.: Contribution à l'étude des splénomégalies de l'enfance, Acta prediat., 1927, supp. 6.

Deposits of lipoid are absent in the vein; hence, phlebosclerosis is probably produced by mechanical changes (portal hypertension), in contrast to the chemical causes which may operate in atherosclerosis. Wohlwill and Holm [13] proved the presence of a mechanical factor by inducing experimental portal hypertension in dogs. However, if cholesterol was then injected intravenously chemical changes were found to be superimposed.

According to the most recent investigation,[14] atheromatous change does not occur in veins and the adaptability of the portal vessels is not influenced by age, hypertrophy occurring in young subjects as frequently as in older ones.

According to Li,[14] two factors are concerned in the production of phlebosclerosis: (1) weakening of the venous wall by nutritional disturbance, degeneration of the media or inflammatory changes and (2) increase of venous pressure. Opinion is still divided as to which is more important and which occurs first [15] though in my estimation the organic changes precede the increased venous pressure. The phlebosclerotic changes of the portal system in portal hypertension are (1) muscular hypertrophy of the media, which occurs first, and (2) intimal thickening with development of longitudinal muscle beneath it.

CLINICAL DIAGNOSIS

The clinical course continues for a long time without hepatomegaly or ascites. Remissions occur and splenomegaly and anemia are present, while recurrent hemorrhages take place. Diagnosis may be suggested by the splenomegaly, which is decreased after a copious hemorrhage, establishment of collateral circulation (fig. 4) [16] and anemia. Hemorrhage occurred during the twelfth and twentieth years of disease in the patient whose case was reported by Hart,[16] and in the cases described by Gruber [15] death occurred thirteen and fourteen years after the first hemorrhage.

Bardach [17] reported a case in which examination revealed varicose veins in the lower portion of the esophagus and the fundus of the

13. Wohlwill and Holm: Experimentelles zur Pfortadersklerose, Verhandl. d. deutsch. path. Gesellsch. **22**:235, 1927.

14. An excellent review and exacting study of the pathogenesis of portal system phlebosclerosis are to be found in an article by Li (Adaptation in Veins to Increased Intravenous Pressure, with Special Reference to the Portal System and Inferior Vena Cava, J. Path. & Bact. **50**:121 [Jan.] 1940).

15. Reich, N. E.: Portal System Thrombosis Occurring in Portal Hypertension, Ann. Int. Med., to be published.

16. Plotz, M., and Reich, N. E.: Esophageal Varices in Portal Hypertension, Pathogenesis and Diagnosis by Roentgenography, Am. J. Digest. Dis. **5**:357 (Aug.) 1938.

17. Bardach, M.: Ein Fall von Pfortaderstenose und Myelothrombophlebitis im Kindesalter, Arch. f. Kinderh. **71**:270, 1922.

stomach. These may be recognized more frequently with a special roentgenographic technic.[16] Posthemorrhagic leukocytosis may obscure the picture. The thrombocytes may be decreased, and this change may in turn be accompanied by purpura.

DIFFERENTIAL DIAGNOSIS

Diseases which must be differentiated are: (1) Banti's syndrome, which offers the greatest difficulty in diagnosis but may be distinguished by the presence of a large liver, ascites, leukopenia, urobilinuria and progressive splenomegaly despite hemorrhages which occur much later in the disease; (2) peptic ulcer; (3) lymphoblastoma; (4) various types of purpura, and (5) disturbances of lipoid metabolism (Gaucher and Niemann-Pick disease).

TREATMENT

Although a cure by recanalization is possible, the condition is progressive because of the increasing portal hypertension.

According to Freund and Schick,[18] the only rational treatment is the early removal of the spleen. This is said to reduce the volume of portal blood by 20 per cent.[19] However, the burden on the collateral circulation cannot be sufficiently removed by late splenectomy, since hematemesis and collateral circulation are found to persist. Hemorrhage from esophageal varicosities may be treated by surgical intervention, based on early diagnosis. At one time or another, McIndoe,[20] Kegaries,[21] Walters and associates,[22] Rousselot [23] and others [24] have recommended the following methods: (1) cauterization through an esophagoscope, (2) ligation of the coronary veins, (3) ligation of the vasa breva and (4) splenectomy, as previously suggested, to reduce the volume of portal blood.

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18. Freund, M., and Schick, B.: Typical Form of Splenomegaly in Childhood: Phlebosclerosis of Portal Circulation, J. Mt. Sinai Hosp. **4**:221 (Nov.-Dec.) 1937.

19. Mayo, W. J.: Review of Five Hundred Splenectomies, Ann. Surg. **68**:409 (Sept.) 1928.

20. McIndoe, A. H.: Vascular Lesions of Portal Cirrhosis, Arch. Path. **5**:23 (Jan.) 1928.

21. Kegaries, D. L.: Venous Plexus of the Esophagus, Surg., Gynec. & Obst. **58**:46 (Jan.) 1934.

22. Walters, W.; Rowntree, L. G., and McIndoe, A. H.: Ligation of Coronary Veins for Bleeding Esophageal Varices, Proc. Staff Meet., Mayo Clin. **4**:146 (May 8) 1929.

23. Rousselot, L. M.: The Role of Congestion (Portal Hypertension) in So-Called Banti's Syndrome, J. A. M. A. **167**:1788 (Nov. 28) 1936.

24. A fuller discussion of portal hypertension may be found in Greene, C. H.; Plotz, M., and Localio, S. A.: Liver and Biliary Tract, Arch. Int. Med. **61**:655 (April) 1939.

COMMENT

In most cases primary portal phlebosclerosis occurs in young persons and is usually congenital. Sclerosis and narrowing of the portal system are present. Some investigators consider the sclerotic process of primary origin,[8] whereas others suggest primary stenosis with secondary sclerosis due to the portal hypertension. According to Li,[14] it is possible to have inflammatory change or sclerosis develop secondary to the increased venous pressure.

Portal hypertension is ordinarily seen in cases of atrophic cirrhosis, but it is recognized as a nonspecific syndrome and may develop in association with any condition in which there is obstruction to the portal flow.[15] This has led to a discussion of Banti's syndrome as a cause of congestive splenomegaly. The concept that Banti's disease, or splenic anemia, is the result of mechanical obstruction to the flow of blood within the portal system, which in turn is due to a variety of primary lesions, is gaining ground rapidly.[25] The interesting thing about phlebosclerosis is that it occurs early in life, before atrophic cirrhosis develops. One point in the clinical differentiation must be stressed. Although there are signs of portal hypertension (esophageal varices and splenomegaly), as in my case, there is no ascites. The absence of ascites is explained on the basis of normal serum protein, as it most frequently develops in patients with hepatic damage and hypoproteinemia. The early age also suggests that the stenosis is primary, with resultant hypertension and finally sclerosis, but this sequence is not proved. It is evident that splenomegaly may be explained on the basis of a congestive process secondary to portal hypertension.

SUMMARY

A case of phlebosclerosis of the portal system is reported.

The use of the term primary portal phlebosclerosis is urged. The condition must be especially differentiated from Banti's syndrome, with which it has long been confused, although the pathologic changes in both may be undifferentiated. The onset at an early age; the absence of ascites and anemia; the presence of leukopenia, sclerosis and narrowing of the portal system, and the sequence of changes are in favor of the former.

It is my opinion that the changes of the venous wall resulting in stenosis of the portal system precede the portal hypertension.

75 Ocean Avenue.

25. Rousselot, L. M.: Congestive Splenomegaly, Bull. New York Acad. Med. **15**:188 (March) 1939; footnote 23. Thompson.[8]

Progress in Internal Medicine

ALLERGY

A REVIEW OF THE LITERATURE OF 1941

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In arranging the many subheadings and topics which have developed in the study of allergy, one finds that some of these are concerned with the basic cause of trouble, others with the development of sensitiveness, others with the mechanisms by which symptoms result, others with the variety of symptoms, and, finally, still others with those changes which have nothing to do with the cause but represent the result or the effect of the primary disturbance.

Last winter I [1] prepared an informal talk along these lines, and the summary was published later in a small bulletin. The chart presented at that time has proved to be a useful arrangement of the various topics and so is presented again here, with some modification. First of all, this chart separates allergy as a study in immunology sharply from asthma, a study in physiology. It is true that often the two go together, so that the study of one involves the other, but, at the same time, it is worth repeating that asthma is not a disease entity, it is merely a symptom. The phrase "All is not allergy that wheezes" still holds. Furthermore, what applies to asthma applies also to hay fever, to eczema, to urticaria, to headache, indeed to all of the other symptoms which have become associated with the term "allergy." None of these symptoms depends always and inevitably on a state of hypersensitiveness.

Dragstedt [2] gives an outline for the study of allergic phenomena, discussing in order the allergen, the antibodies, the sensitized cells, the liberated products and the responsive tissues. Let us review the current literature in the light of my chart and with an eye on Dr. Dragstedt's outline.

ALLERGY

THE ALLERGIC STATE

The allergic state is real. That explains why it is that only a small proportion of those persons exposed to an occupational dust become sensitive to the new foreign substance; it explains why only a small

1. Rackemann, F. M.: Allergy: A Problem in Immunology; Asthma: A Problem in Physiology, Bull. New England M. Center **3**:199, 1941.
2. Dragstedt, C. A.: Anaphylaxis and Allergy, Ann. Int. Med. **13**:248, 1939.

proportion of the population has hay fever. Persons with an allergic constitution have the capacity for the development of sensitiveness. This is an old story illustrated by many experiences; another is the case reported by Way.[3] Dog asthma developed in a boy aged 15 and lasted until the dog died, four years later. For eleven years the young man was well, until, at the age of 30, he became interested in tropical fish. Asthma recurred in monthly attacks, which were found due to a newly acquired sensitiveness to the dust of dried water fleas (Daphnia) used as a fish food.

The Problem *

Allergy (Immunology)	Asthma (Physiology)
Nature of the allergic state	Spasm; edema
An "allergic person": one with a capacity for sensitiveness to develop, due to heredity (?), endocrine factors (?), vitamins (?)	Allergic reaction
	"Intrinsic" asthma
	Irritation from gas or cold air?
	(Reflex from nose?)
Five criteria	Exudate
Typical pathologic changes	"Intrinsic" asthma
Multiple symptoms	Bronchitis; tuberculosis; effect of gases
Family history of allergy	Obstruction
Eosinophilia	Foreign body
Positive cutaneous reactions	Intrabronchial tumor
Development of sensitivity	Carcinoma
(Exposure; "low resistance")	Gumma
Passive	Extrabronchial tumor
Placental transmission	Sarcoid
Transfusion	Enlarged glands
Active	(Hodgkin's disease)
Inhalation of dusts	Tuberculoma
Ingestion of foods or drugs	Emphysema
Injection of foreign substances	"Pulmonary insufficiency"
(Chemistry of antigens)	Primary emphysema
Locus of symptoms	Secondary emphysema
Mode of contact	Chronic passive congestion
Local injuries	Cardiac: failure of the left side of the heart
Mechanism of symptoms	Corpulmonale: failure of the right side of the heart
Release of histamine by an antigen-antibody reaction	
(Acetylcholine?)	
Factors changed as a result of symptoms	
Blood level of histamine	
Eosinophil count	
Metabolism of salt and water	

* Adapted from Rackemann.[1]

Heredity is dominant in this state, as emphasized again by Ratner and his associates.[4] Landsteiner and Chase [5] have been able to breed guinea pigs in such a way that one strain will be much more sensitive to poison ivy than another strain. In another experiment Chase [6] bred

3. Way, K. D.: Water Flea Sensitivity: Case Report, J. Allergy **12**:495, 1941.

4. Ratner, B.; Silberman, D. E., and Greenburgh, J. E.: Allergy in Childhood: IV. Does Heredity Determine the Age of Onset? J. Allergy **12**:272, 1941.

5. Landsteiner, K., and Chase, M. W.: Breeding Experiments in Reference to Drug Allergy in Animals, Proc. Internat. Cong. Microbiol., 1940, p. 772.

6. Chase, M. W.: Inheritance in Guinea Pigs of the Susceptibility to Skin Sensitization with Simple Chemical Compounds, J. Exper. Med. **73**:711, 1941.

guinea pigs with a cutaneous sensitiveness to 2-4-dinitrochlorobenzene and then found that by careful breeding of his animals he could produce a strain of more sensitive and a strain of less sensitive guinea pigs. The last observation shows that heredity may be a factor in local cutaneous allergy as well as in the more general sensitiveness called "atopy."

What else is concerned? One thinks of internal secretions, but so far there is little evidence to suggest that one or the other of the endocrine glands is concerned with the allergic constitution. Barnes,[7] for example, studied the basal metabolism and the cholesterol content of the blood of 25 patients with allergy and 25 nonallergic control subjects, but the results were normal throughout both groups. The adrenal glands or variations in the output of epinephrine might be abnormal. Bloor and Bullen[8] have a new chemical method for determining the amount of epinephrine in the venous blood, and one can hope that later they will present data on the results of its use in a large series of cases.

The vitamins have been considered as a fundamental factor in the development of allergy and in the production of symptoms, and the problem is under investigation in the allergy laboratory of the Massachusetts General Hospital at this time. The literature on vitamin C in its relation to infectious disease as well as to anaphylactic shock and to allergy is voluminous and contains many papers dealing with experiments on animals but has relatively few observations on the concentration of ascorbic acid (vitamin C) in various clinical states. Recently, however, Goldsmith, Ogaard and Gowe[9] reported that for persons who had no condition known to be associated with subnormal vitamin C nutrition the ascorbic acid in the blood plasma varied from 0.07 to 2.40 mg. per hundred cubic centimeters, with a mean value of 0.602 ± 0.049 mg. In 29 patients with asthma, however, this plasma ascorbic acid varied from 0.02 to 1.87 mg. per hundred cubic centimeters, with a mean value of 0.410 ± 0.051 mg. The authors describe the good results which followed the administration of ascorbic acid in considerable amounts to their patients, the best method being to inject the material intravenously in doses as large as 1 Gm., a quantity which resulted in the raising of the blood level of ascorbic acid to 7.0 mg. per hundred cubic centimeters in about twenty minutes. After that it was comparatively easy to maintain a high level by the feeding of fairly large amounts

7. Barnes, M. C.: The Thyroid in Allergy, South. M. J. **33**:1310, 1940.

8. Bloor, W. R., and Bullen, S. S.: The Determination of Adrenalin in Blood, J. Biol. Chem. **138**:727, 1941. Bullen, S. S., and Bloor, W. R.: Studies in Epinephrine: Recovery of Epinephrine Injected Intravenously and Subcutaneously, J. Allergy **12**:564, 1941.

9. Goldsmith, G. A.; Ogaard, A. T., and Gowe, D. F.: Vitamin C (Ascorbic Acid): Nutrition in Bronchial Asthma; An Estimation of the Daily Requirement of Ascorbic Acid, Arch. Int. Med. **67**:597 (March) 1941.

of the vitamin. It was interesting that patients with asthma could not maintain the level as well as could the nonasthmatic controls. As for the effect of treatment, one must recognize that when a large dose like this is injected intravenously in an asthmatic person, it is not impossible that the effect is more like that of a drug than like that of a food.

Cormia [10] reports that when massive doses of ascorbic acid were given first intravenously and then by mouth to patients in whom previously severe dermatitis had developed after the administration of arsphenamine an arsenical could be tolerated without difficulty. He could not show, however, that those patients whose blood level of vitamin C was low could be sensitized any easier than could those with a normal level of the vitamin in the blood. He reasoned that some factor in addition to the vitamin is involved. Bronfenbrenner and his associates [11] found that when guinea pigs are deficient in vitamin C sensitivity can be developed by feeding an antigen and that later shock will occur if the foreign protein is fed again. In the discussion of this paper Sulzberger called attention to his own previous observations that sensitiveness of the skin could be produced in certain lots of guinea pigs better than in others and that one of the differences was in the fodder on which the animals were fed. The interesting point, however, is that scurvy causes lesions in mucous membranes, which makes them more permeable and thus permits the passage of foreign protein into the blood. Meantime, however, Friedman [12] found that the muscles of scorbutic guinea pigs are much less sensitive to histamine than those of normal guinea pigs. Indeed, the minimal stimulating dose for scorbutic muscle in the Dale bath was of the order of a dilution of 1 : 10,000,000, whereas the normal muscle reacted to histamine in a dilution of 1 : 10,000,000,000. The latter was a thousand times more sensitive. Other papers deal with the use of vitamin C in clinical treatment, as a drug rather than as an essential food. One should note that ascorbic acid is a reducing agent.

DEVELOPMENT OF SENSITIVITY

Sensitization may be either active or passive.

Passive Sensitization.—The occurrence of this type of sensitization as a result of transfusion has been reported, but the cases are rare.

10. Cormia, F. C.: Post Arsphenamine Dermatitis: The Relation of Vitamin C to the Production of Arsphenamine Sensitiveness and Its Use as an Adjunct to Further Arsphenamine Therapy in Patients with Cutaneous Hypersensitiveness to the Arsphenamines, J. Invest. Dermat. **41**:81, 1941.

11. Bronfenbrenner, J.; Hetter, D. M.; Love, F. M., and Burnett, J. M.: Experimental Alimentary Allergy and Its Prevention, J. Allergy **11**:466, 1940.

12. Friedman, H. J.: Effect of Vitamin C Deficiency upon Smooth Muscle Responsiveness to Non-Specific Stimulation, J. Allergy **12**:221, 1941.

Loveless [13] could collect only 6 reported cases, but to them she has added 3 cases in which experimental transfusions were made with blood from donors ill with ragweed hay fever. Within a few hours cutaneous tests, ophthalmic tests and nasal tests all gave positive reactions and skin-sensitizing antibodies were demonstrable in the blood serum of the recipients. The placental transmission of antibodies is much more likely to occur, and a new paper on the subject is one by Sherman, Hampton and Cooke,[14] The cord blood of newborn infants whose mothers were sensitive to pollen was tested for skin-sensitizing antibodies, but none was found. Extracts of the placenta in physiologic solution of sodium chloride failed to show antibodies. When, however, the cord serum was mixed with ragweed and then its effect compared with that of similar mixtures of control serum and ragweed, there was evidence of partial blocking. The retest of normal cutaneous sites passively sensitized with these mixtures gave less reaction with the cord serum than with the control blood, an indication of the presence of a mechanism by which the skin-sensitizing antibody was prevented (blocked) from combining with the admixed ragweed. Later on, however, when the infants were 3 to 6 months old, similar studies showed that the block has disappeared. The data in this experiment correspond with known facts concerned with the transmission of typhoid agglutinins and other immune principles and support the belief that the blocking effect depends on a true antibody.

Active Sensitization.—This type of sensitization is common enough. It may occur through the inhalation of dust or the ingestion of foods or drugs, or it may follow the injection of foreign substances. When exposure is slight, as in industry or in the household, it becomes evident that this exposure must continue over a definite interval before sensitiveness will develop. In my review of last year [15] two interesting papers were mentioned. Phillips [16] found that sensitiveness to the pollen of the sugar beet sufficient to cause hay fever did not occur in persons living near Phoenix, Ariz., until sugar beets had been cultivated in that part of the country for at least two years. Clarke and Leopold [17] reported that the

13. Loveless, M. H.: Immunological Studies of Pollinosis: II. Passive Sensitization of Man Through Transfusion, J. Immunol. **41**:15, 1941.

14. Sherman, W. B.; Hampton, S. F., and Cooke, R. A.: The Placental Transmission of Antibodies in the Skin Sensitive Type of Human Allergy, J. Exper. Med. **72**:611, 1940.

15. Rackemann, F. M.: Allergy: Review of the Literature of 1940, Arch. Int. Med. **67**:207 (Jan.) 1941.

16. Phillips, E. W.: Time Required for the Production of Hay Fever by Spores of a Newly Encountered Fungus, Johnson Grass Smut, J. Allergy **12**:24, 1940.

17. Clarke, J. A., Jr., and Leopold, H. C.: Effect of Pollen Contact upon Age of Onset of Hay Fever, J. Allergy **11**:494, 1940.

interval for the development of hay fever was quite the same for immigrants arriving in this country as it was for native Americans. In the one case the interval began on landing; in the other it began at birth. Drug allergy as a whole will be discussed later, but many cases of this type are pertinent to the present topic, for they emphasize that exposure often continues for a time before symptoms appear.

Sensitiveness Acquired by Inhalation: This type of sensitivity was recognized by Bohner and associates [18] in a group of printers who used a spray of acacia as an "offset" in a printing process. Ten persons were observed, and it is interesting that they had been exposed for periods varying from two weeks to twelve months before asthma developed. King [19] has recognized another group of printers with precisely the same difficulties.

Sensitiveness Acquired by Ingestion of Foods or Drugs: This type is, of course, more common. Davidson and Bullowa [20] describe the case of a young Negro who was given 12 Gm. of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) during an attack of pneumonia, with no particular reaction. Eleven days later, however, 5 Gm. of sulfamethylthiazole (2-[paraaminobenzenesulfonamido]-methylthiazole) was given, and within three hours generalized itching, with a scarlatiniform eruption, fever and chills, developed. Another case is reported by Kennedy and Finland,[21] but it is less typical. A woman aged 38 was treated with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) for subacute bacterial endocarditis. Five days later a few petechiae appeared, and in two weeks the spleen became tender with a friction rub over it. In three weeks her leukocyte count was found to be only 1,200 per cubic millimeter, and she died of fatal granulocytopenia. In this case there was no history of her having taken any of the sulfanilamide drugs before. The attack was evidently a sort of serum disease.

Sensitiveness Acquired by Injection of Foreign Substances: This occurs more often than one would expect. The literature this year contains at least three references. Laws [22] reports the case of a woman aged 72 who was given thiamine hydrochloride daily for ten days and later every week. In about five months she noticed that each dose

18. Bohner, C. B.; Sheldon, J. M., and Trenis, J. W.: Sensitivity to Gum Acacia, with a Report of Ten Cases of Asthma in Printers, J. Allergy **12**:290, 1941.

19. King, J. J.: Asthma and Allergic Rhinitis in Printers Due to Gum Arabic (Acacia) in Non-Offset Spray, J. Med. **22**:119, 1941.

20. Davidson, A., and Bullowa, J. G.: Acquired Hypersensitivity to Sulfapyridine and Sulfamethylthiazole, New England J. Med. **223**:811, 1940.

21. Kennedy, P. C., and Finland, M.: Fatal Agranulocytosis from Sulfathiazole, J. A. M. A. **116**:295 (Jan. 25) 1941.

22. Laws, C. L.: Sensitization to Thiamine Hydrochloride, J. A. M. A. **117**:176 (July 19) 1941.

produced a sneeze, and in seven months a dose was followed within thirty minutes by swelling of her eyes and lips, by generalized urticaria and, finally, by asthma. A cutaneous test with thiamine hydrochloride resulted in a large local reaction of the immediate urticarial type. Wiseman and Gillette [23] report the case of a patient with syphilitic meningitis who had received eighty doses of tryparsamide intravenously. After this treatment came an interval of two years without further attention, and then when the drug was resumed the second dose caused sudden amblyopia, without, however, other manifestations. Here was evidence of a specific sensitiveness localized to a particular tissue but artificially produced. Hansen [24] reports the case of a woman with asthma who was treated on five occasions by the injection of a 1 per cent solution of procaine hydrochloride into the stellate ganglion. The clinical results were excellent at first, but when the sixth dose was given respiratory paralysis and death occurred within ten minutes.

Contact Dermatitis: This must by its nature depend on local sensitiveness induced by previous local contacts. Zakon [25] had a patient who had worn an elastiglass wristband for eight weeks before a bullous dermatitis appeared, and there are many reports of similar cases except that in most of them the time interval is not stated. That local injury may determine the rate of development as well as the locus of sensitiveness is a point to be discussed later. In guinea pigs Landsteiner and Chase [26] were able to induce a sensitiveness to quinine by repeated applications of the drug in an oily vehicle. But it was induced more easily if a particular area had been inflamed by a local irritant. Finally, Bonnevie [27] calls attention to the danger of sensitization as a result of patch tests. This danger, however, is not great, for it was recognized in only 40 of 50,000 routine tests. Finally, one should note with Silverberg and Heimann [28] that cutaneous tests, whether made by the scratch or by the patch method, may give positive reactions, even though no clinical symptoms accompany them. A small series of fur workers

23. Wiseman, J. R., and Gillette, D. F.: Drug Allergy with Special Reference to Tryparsamide, New York State J. Med. **41**:1, 1941.

24. Hansen, J. L.: Death from Procaine Hydrochloride in Connection with Infiltration of Procaine Hydrochloride into the Stellate Ganglion, Ugesk. f. læger **103**:159, 1941.

25. Zakon, S. J.: Bullous Dermatitis from Elastiglass, Arch. Dermat. & Syph. **43**:548 (March) 1941.

26. Landsteiner, K., and Chase, M. W.: Quinine Hypersensitivity in Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **46**:223, 1941.

27. Bonnevie, P.: Etiologic-Pathogenetical Experience of Professional Skin Diseases and a View to Their Prophylaxis, Acta dermat.-venereol. **20**:632, 1939.

28. Silverberg, M. G., and Heimann, H.: Studies with Paraphenylenediamine in Fur Workers, J. Invest. Dermat. **4**:1931, 1941.

were given patch tests with paraphenylenediamine, and 4 of 10 gave positive reactions, even though they had never had any clinical signs of dermatitis.

The Chemistry of Hypersensitiveness: Several papers indicate that small differences in the chemical constitution of certain substances make a difference in the readiness with which sensitiveness to them is developed as well as in the production of symptoms. Arsenical dermatitis may result from the treatment with neoarsphenamine, but Schoch, Alexander and Long [29] found that if mapharsen was substituted no further trouble would follow. According to Franks and Fisher,[30] however, substitution of tryparsamide in the treatment of 2 patients produced recurrences of the dermatitis. The chemical relations are complex.

The sulfanilamide drugs are every day more important. Goodman and Arthur [31] observed a Negro in whom an eruption developed always in the same place after each dose of sulfanilamide. Sulfapyridine, however, was tolerated without ill effects. The other day I saw a patient of Dr. C. Lyons with an infection of the urinary tract whose symptoms were made worse by each and every one of the sulfanilamide drugs. In this case the sensitiveness was evidently due to a common basic factor and not to any particular or specific complex in the molecules. Cutaneous tests showed no reaction whatever to heavy suspensions of the various sulfanilamide drugs.

Direct chemical studies on different allergens reported during the year are few, and the results are still not entirely satisfactory. There has been much work done on the chemistry of ragweed, but so far no one has been able to isolate the active substance with any degree of assurance. In the allergy clinic of the Massachusetts General Hospital Dr. J. M. Newell [32] has studied the several fractions resulting from treatment of aqueous extracts of ragweed with various concentrations of ammonium sulfate or with various dilutions of alcohol. Each of these fractions was obtained in a relatively pure state by a technic which was as efficient as possible, the work being done in the Laboratory of Biological Chemistry at the Harvard Medical School through the courtesy of Prof. Edwin J. Cohn. In spite of the careful manipulation, the active

29. Schoch, A. G.; Alexander, L. J., and Long, W. E.: Mapharsen in the Treatment of Forty Patients Following Arsphenamine Dermatitis, Arch. Dermat. & Syph. **42**:919 (Nov.) 1940.

30. Franks, A. G., and Fisher, S.: Sensitization to Arsenical Compounds, Arch. Dermat. & Syph. **42**:808 (Nov.) 1940.

31. Goodman, M. H., and Arthur, R. C.: Fixed Eruptions (Report of an Unusual Condition Due to Sulfanilamide), Arch. Dermat. & Syph. **43**:692 (April) 1941.

32. Newell, J. M.: Unpublished data.

principle demonstrable by cutaneous testing was present in most of the fractions, though varying somewhat in its quantity.

Stull, Sherman and Hampton [33] made an aqueous extract of ether-defatted ragweed and then precipitated it with a 50 per cent solution of ammonium sulfate. The precipitate was designated fraction 1 and was found to contain most of the nitrogen. When the material was fully saturated with ammonium sulfate a second precipitate was obtained, which was called fraction 2. This contained relatively little total nitrogen but still had a quantity which could be precipitated by phosphotungstic acid as protein nitrogen. Furthermore, this fraction gave a positive reaction to the Molisch test, which indicated the presence of carbohydrates. When these two fractions were tested on ragweed-sensitive patients the results were somewhat variable, although most patients reacted about equally to each of them. By crossed experiment, however, the authors found that each fraction had its own antigenic specificity, as well as some crossed relationship to the other fraction. Thus, when fraction 2 was mixed in a test tube with serum from a patient skin sensitive to both fractions, the mixture was still able to sensitize normal skin to fraction 1, an indication that neutralization was not complete. In a more recent paper Sherman and Hebald [34] report that when patients were more sensitive to fraction 2 than to fraction 1 general constitutional reactions were more likely to occur during treatment with the corresponding material.

Rockwell [35] digested ragweed extract with pepsin at a p_H of 7.5, but in spite of this treatment ragweed-sensitive persons still reacted well to the extract. This experiment shows, incidentally, that during oral treatment little if any of the pollen antigen can be destroyed by the enzymes of the stomach. Chemical studies on the cottonseed allergen gave results of a similar kind. Coulson, Spies and Stevens [36] separated three fractions by various methods, including treatment with trinitrophenol, and found that each of them elicited positive cutaneous reactions from cottonseed-sensitive patients. The allergic component seemed to be a heat-stable protein, which was evidently a preformed constituent of the cottonseed embryo.

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33. Stull, A.; Sherman, W. B., and Hampton, S. F.: Antigenic Fractions in Ragweed Pollen: I. Water-Soluble Fractions, J. Allergy **12**:117, 1941.

34. Sherman, W. B., and Hebald, S.: The Importance of Certain Antigenic Fractions of Ragweed Pollen in Relation to Constitutional Reactions During Treatment, J. Allergy **12**:605, 1941.

35. Rockwell, G. E.,: The Effects of Enzymes on Ragweed Pollen and Studies on the Iso-Electric Point of Low-Ragweed Antigen, J. Immunol. **41**:225, 1941.

36. Coulson, E. J.; Spies, J. R., and Stevens, H.: The Immunochemistry of Allergens: I. Anaphylactogenic Properties of a Protein Component of Cottonseed, J. Immunol. **41**:375, 1941.

When Cooke and his colleagues [37] found that the reactions to tetanus toxoid were caused by the Witte peptone in the material, it occurred to them that possibly other primary and secondary proteoses might give rise to allergic reactions and so explain the presence of a clinical sensitiveness in the absence of a positive cutaneous reaction to the whole material. They therefore precipitated a variety of substances, first by half saturation and later by full saturation with ammonium sulfate. They used chicken meat, the whey and casein of milk, beef and beef fibrin, as well as egg albumin and wheat gliadin, and they found that many of these materials were quite capable of causing specific reactions when added to the isolated uteri of guinea pigs sensitized to them. In each case the reaction was specific for the particular proteose and quite different from the specificity of the original material. On the other hand, certain of the proteoses failed entirely to sensitize the animals. Further experiments along this line are awaited with interest, for they may help to explain the occurrence of clinical sensitiveness to a food in patients who do not give positive cutaneous reactions to the extract of that food. It may well be that the sensitiveness is to the split product and not to the whole food.

LOCUS OF SYMPTOMS

The locus of symptoms depends usually on the mode of contact. Chemicals of various sorts are used in industries and may cause trouble, usually in the form of a dermatitis, from direct contact. Pollens and dusts, like animal danders or the dust of kapok pillows, cause trouble through inhalation, and symptoms develop in the eyes, the nose and the chest (bronchi). But it is interesting to find that a substance like arsenic can produce symptoms of different sorts in different persons, even though they are all exposed in much the same way. Last winter I [38] reviewed the literature on drug allergy and found a tremendous variation in the manifestations of allergy to drugs of all sorts. Arsenic, for example, may produce a local contact dermatitis either from treatment of vaginitis with an arsenic compound or through contamination of the fingers with a solution of arsphenamine. The generalized dermatitis which occurs during antisyphilitic treatment is common enough. But then one finds that in other patients with similar treatment a reaction develops which is not a cutaneous disease at all but a blood dyscrasia,

37. Cooke, R. A.; Hampton, S. F.; Sherman, W. B., and Stull, A.: Allergy Induced by Immunization with Tetanus Toxoid, J. A. M. A. **114**:1854 (May 11) 1940. Stull, A., and Hampton, S. F.: A Study of the Antigenicity of Proteoses, J. Immunol. **41**:143, 1941.

38. Rackemann, F. M.: Allergy, with Special Reference to Drug Allergy, New England J. Med. **224**:688, 1941.

like purpura or granulocytopenia. In some an attack of asthma appears. A condition of the same sort is being recognized already as caused by sensitiveness to sulfanilamide or to one of its relatives. Furthermore, why does one patient become sensitive to timothy and have hay fever in June, whereas the next one is sensitive to ragweed and has hay fever in August? One wonders about the possibility of local injury at the time of exposure; in the case of hay fever perhaps a bad cold or some other temporary disturbance lowers the resistance of the local mucous membrane in the nose. So far, the reason for all this is not at all clear, but the case reports in the field of drug allergy tend to broaden one's approach to the problem. The fact that certain tissues of the body can become more sensitive than others would seem to be established.

MECHANISM OF SYMPTOMS

Primarily, the symptoms of allergy depend on the reaction which takes place when the foreign substance reaches the specific antibodies in the sensitized cells. In the case of a local contact dermatitis, antibodies are not demonstrable in the blood and the hypersensitiveness is not transferable by means of the so-called reagin. In other, more typical conditions, such as hay fever and asthma, the fact that transfer is possible demonstrates a general sensitiveness of the whole body, with antibodies in the blood. So far it is thought that these antibodies are quite different from precipitins, but now comes evidence, presented by Cohen and Weller,[39] that the difference may be more apparent than real. Employing a colloidal suspension of collodion particles, they were able to treat aqueous extracts of pollen so that when serum from sensitive patients was added to the preparation a precipitate would result. In last year's review I [15] discussed the mechanism by which the good results of the treatment of hay fever might be explained. Sherman,[40] Loveless [41] and, more recently, Scully and Rackemann [42] have studied this question further, but, unfortunately, none of them has been able to demonstrate a relation between the degree of improvement and the concentration of the heat-stable blocking antibodies which appear to develop after treatment.

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39. Cohen, M. B., and Weller, R. R.: Precipitins in the Sera of Patients with Clinical Allergy, J. Allergy **12**:242, 1941.

40. Sherman, W. B.: Changes in Serological Reactions and Tissue Sensitivity in Hay Fever Patients During the Early Months of Treatment, J. Immunol. **40**: 289, 1941.

41. Loveless, M. H.: Immunological Studies of Pollinosis: I. The Presence of Two Antibodies Related to the Same Pollen Antigen in the Serum of Treated Hay Fever Patients, J. Immunol. **38**:25, 1940.

42. Scully, M. A., and Rackemann, F. M.: Studies on the Blocking Antibody of Cooke in the Treatment of Hay Fever, J. Allergy **12**:549, 1941.

How does the antigen-antibody reaction produce symptoms? Supposedly it does this by causing a liberation of histamine from the injured cells.

Histamine.—Last year the current literature on histamine and histaminase was reviewed [15] with some care, and the section ended with a quotation from Best and McHenry [43]: "There is no physiologic basis on which to rest the clinical use of histaminase." Meantime, however, the work goes on, and a new series of papers has accumulated. A simple, well written and satisfactory summary of the relation of histamine to anaphylaxis and allergy is presented by Rose,[44] who touches on such topics as the distribution and state of histamine in the body, the effect of the administration of histamine, the comparison of histamine shock and anaphylactic shock, the evidence for the release of histamine in anaphylaxis and the possible relation of histamine to allergic phenomena. As for histaminase, the evidence for its effectiveness is conflicting. Some papers show that the enzyme histaminase is ineffective. Rose and Browne [45] have repeated their experiments on histamine shock in guinea pigs and now state that previous treatment with histaminase does not reduce the degree of histamine shock as previously reported. Alexander and Bottom [46] tried to protect guinea pigs against histamine shock and anaphylactic shock by treating them with histaminase, but with no success. On the other hand, Barlow and Hamburger [47] express the belief that a small percentage of their guinea pigs were protected against anaphylactic shock and against histamine shock by pretreatment with histaminase. Karady [48] also could prevent anaphylactic shock by pretreatment with histamine.

Knoll and Beinhauer [49] gave histaminase intravenously to sensitized guinea pigs just before a shocking dose of egg albumin, but the reaction occurred regardless of the preliminary treatment. The injection of histamine stimulates the secretion of acids in the stomach, and the action is easily studied. To dogs with a Heidenhain pouch Atkinson and

43. Best, C. H., and McHenry, E. W.: Note on Histaminase, Canad. M. A. J. **43**:163, 1940.

44. Rose, B.: The Relation of Histamine to Anaphylaxis and Allergy, McGill M. J. **10**:2, 1940.

45. Rose, B., and Browne, J. S. L.: Effect of Histaminase Pretreatment on Histaminase Shock in Guinea Pigs, J. Immunol. **41**:409, 1941.

46. Alexander, H. L., and Bottom, D.: The Failure of Histaminase to Protect Guinea Pigs Against Histamine and Anaphylactic Shock, J. Immunol. **39**:457, 1940.

47. Barlow, O. W., and Hamburger, E.: The Influence of Histaminase on the Course of Anaphylaxis and Histamine Shock in Guinea Pigs, J. Allergy **12**:346, 1941.

48. Karady, E. S.: Histamine Tolerance and Anaphylactic Death in Sensitized Guinea Pigs, J. Immunol. **41**:1, 1941.

49. Knoll, A. F., and Beinhauer, L. G.: Experimental and Clinical Observations with Histaminase, Arch. Dermat. & Syph. **42**:896 (Nov.) 1940.

co-workers [50] gave histaminase, but they were unable to demonstrate any inhibition of the usual gastric response when histamine was given shortly afterward.

Clinical reports are a little more encouraging! With reference to cold allergy, Roth and Horton [51] repeat their assertion that treatment with histaminase can protect against the syndrome which follows the immersion of the hands in cold water. Cherry and Prickman [52] express the opinion that if histaminase is given within twenty-four hours after the onset of serum disease the severity of the symptoms is modified. Moreover, 9 patients were given the enzyme prophylactically at the time when the serum was administered: In 4 of them serum disease did not occur, and in the other 5 the reaction was mild. The difficulty is that "normal" serum disease is so irregular in its severity. Simon [53] had a more precise technic. Using the intradermal response to histamine as a test, he injected a solution of histaminase into the site sometimes before and sometimes after the injection of histamine, but in neither case could he show that histaminase was effective in modifying the response to histamine.

Studies on histamine itself are more interesting. First of all, it becomes clear that the effect of histamine is not related necessarily to the concentration in the blood. Rose [54] could not observe any regular increase in the histamine level of the blood during various allergic conditions. In certain acute states, such as an attack of angioneurotic edema, there was often a decrease in the value; in cases of asthma the values fluctuated to a considerable extent. Randolph and Rackemann [55] observed similar changes in a much smaller series of cases. Even when the symptoms, such as a rapid pulse, flushing, headache and low blood pressure, were produced directly by a dose of histamine administered subcutaneously, it was still impossible for Rose [56] to demonstrate any

50. Atkinson, A. J.; Ivy, A. C., and Bass, V.: The Effect of Histaminase on the Gastric Secretory Response to Histamine, Am. J. Physiol. **132**:1, 1941.

51. Roth, G. M., and Horton, B. T.: Histaminase: Physiologic Effects on Man and Its Therapeutic Value in Medicine, Bull. New York Acad. Med. **16**:570, 1940.

52. Cherry, J. H., and Prickman, L. E.: The Treatment and Prevention of Serum Sickness by the Use of Histaminase, Proc. Staff Meet., Mayo Clin. **16**:38, 1941.

53. Simon, F. A.: Experiments with Histaminase, J. Invest. Dermat. **3**:299, 1940.

54. Rose, B.: Studies on Blood Histamine in Patients with Allergy: II. Alteration in the Blood Histamine in Patients with Allergic Disease, J. Clin. Investigation **20**:419, 1941.

55. Randolph, T. G., and Rackemann, F. M.: The Blood Histamine Level in Asthma and in Eosinophilia, J. Allergy **12**:450, 1941.

56. Rose, B.: Production of Symptoms by Subcutaneous Injection of Histamine Without Increase of the Blood Histamine, Science **92**:454, 1940.

increase of histamine in the peripheral blood. In a few cases of dermographia, however, he [57] could show that after stroking the skin an immediate, though slight, rise in the histamine content of the blood occurred, but it was evanescent.

Treatment with Histamine.—Histamine may have a place as a therapeutic agent. Capps and Young [58] observed a patient who was extremely sensitive to light and exhibited urticaria and later circulatory collapse on exposure to a carbon arc light. Further exposure caused an increase of his gastric acids. Treatment with histamine produced a virtual cure. Farmer [59] had fair results in treating asthma and yasomotor rhinitis by increasing the tolerance to histamine. Alexander [60] makes an interesting observation: It is his experience that neither histamine nor histaminase has any value in the treatment of extrinsic allergy, in which the cause is a specific sensitiveness. But in other conditions, such as urticaria or, especially, intrinsic allergy, histamine may be helpful. The differences between the response of the two types of allergy raises the question whether the H substance (histamine-like substance) released in true allergy is qualitatively the same as that released in the other states.

Ménière's Disease: In cases of this disease histamine treatment may be of value. Horton,[61] of the Mayo Clinic, gave daily intravenous injections of 1.0 mg. of histamine base (2.75 mg. of histamine diphosphate or 1.88 mg. of histamine acid phosphate) diluted in 250 cc. of physiologic solution of sodium chloride, allowing it to run in slowly. In 49 patients the relief was prompt, and after a few days the intravenous method could be omitted and the gain maintained by subcutaneous injection of 0.1 to 0.2 mg. of histamine base two or three times a week. In 1939 Horton, MacLean and Craig [62] described a form of unilateral headache different from migraine. It is not inherited; it begins late, not early, in life, and it is not accompanied by nausea, by vomiting or by visual disturbances. The attacks begin and end suddenly and are of short, about an hour's, duration. It comes on usually at night, and the patient

57. Rose, B.: Studies in Blood Histamine in Cases of Allergy: I. Blood Histamine During Wheal Formation, J. Allergy **12**:327, 1941.

58. Capps, R. B., and Young, R. H.: Hypersensitivity to Light: Studies on an Unusual Case Treated Successfully with Histamine, J. Clin. Investigation **19**:778, 1940.

59. Farmer, L.: Histamine Treatment of Allergic Diseases: I. Asthma and Vasomotor Rhinitis, J. Lab. & Clin. Med. **26**:802, 1941.

60. Alexander, H. L.: Treatment of Allergic Disorders with Histamine and Histaminase, J. Lab. & Clin. Med. **26**:110, 1940.

61. Horton, B. T.: The Use of Histamine in Ménière's Disease, Surg., Gynec. & Obst. **72**:417, 1941.

62. Horton, B. T.; MacLean, A. R., and Craig, W. McK.: A New Syndrome of Vascular Headache: Results of Treatment with Histamine; Preliminary Report, Proc. Staff Meet., Mayo Clin. **14**:257, 1939.

obtains relief by standing upright and by exercising. This type of headache is due to vasodilatation, not to constriction, of the cerebral vessels. It can be induced by histamine and relieved by the administration of epinephrine. It is relieved also by the application of cold water. This year Horton [63] reports on 72 patients suffering from what he now calls "histaminic cephalgia." Whereas histamine can induce the headache, small repeated doses given twice daily are an effective treatment. The doses should begin with 0.25 cc. from an ampule of histamine diphosphate, of which 0.275 mg. is equivalent to 0.10 mg. of histamine base, and the quantity should be reduced if flushing or headache occurs. After ten days (twenty doses), if all is well, the intervals can be lengthened so that maintenance doses are given twice, or maybe only once, a week. Of 51 patients with typical histamine cephalgia who were treated in this way, 48 had complete relief; the other 3 were not heard from. Baker [64] has recognized headache of this type in 15 patients and has given relief to 14 by treatment with histamine.

HAY FEVER

New Pollen Surveys.—Studies of this type are always welcome. Raddis [65] reports on pollens of Hawaii. The cycad tree gives off large quantities of pollen, but positive cutaneous reactions to it have not been observed. Grasses are present. The pollens of sugar cane, the mango and some of the palms cause some trouble in a few cases. Pollen counts are low. From Palestine Gutmann [66] writes that hay fever is only of the spring type, occurring from the end of February to the end of May, when the rain makes the grass grow. The island of Bermuda is relatively free of pollen. Gay, Curtis and Norris [67] state that the Bermuda cedar pollen is found on slides at all times of year except the fall months, September, October and November, but that the peak of the cedar pollination comes in March. In the summer, beginning in May, a few grasses are in flower, but not enough to cause trouble. There is no ragweed in Bermuda. Durham [68] has visited Alaska. In early July there is a little grass pollen in Juneau and Fairbanks, and in August

63. Horton, B. T.: The Use of Histamine in the Treatment of Specific Types of Headache, J. A. M. A. **116**:377 (Feb.) 1941.

64. Baker, B. M.: The Treatment of Periodic Headache by Injections of Histamine, Tr. A. Am. Physicians **55**:294, 1940.

65. Raddis, L. H.: Botanical Considerations of Some Pollens of Hawaii in Relation to Allergy, Tr. Hawaii Territor. M. A. **1**:75, 1939.

66. Gutmann, M. J.: The First Report on Hay Fever in Palestine, J. Allergy **12**:182, 1941.

67. Gay, L. N.; Curtis, H., and Norris, T.: A Pollen Survey of the Islands of Bermuda, Bull. Johns Hopkins Hosp. **68**:179, 1941.

68. Durham, O. C.: Atmospheric Allergens in Alaska, J. Allergy **12**:307, 1941.

the pine trees pollinate. A few fungi, mostly rusts, are to be found, but in Alaska there is no ragweed. From South America come two reports by Ruiz Moreno and his co-workers [69] and a paper by Walker and Carron.[70] The eucalyptus tree is important in Argentina, and further inland there is a bush, Celtis tala, which begins to pollinate in September and reaches a maximum in November and December. The weed Parthenium has a composite flower, with large amounts of pollen. Pratt and associates [71] have made a careful study of pollen in the Boston area, comparing the counts made at four different stations in the city. The resulting curves are similar, but they cannot be superimposed consistently, a fact which indicates that local vegetation and local wind currents around buildings and trees are important. Figures for pollen counts need not be taken always at their face value.

Treatment of Hay Fever.—There are new ideas on extracts for the treatment of hay fever. Naterman [72] precipitates his pollen extracts with tannic acid to make a "ragweed tannate," which he thinks gives better results. Spain and co-workers [73] add 4 parts of gelatin to 1 part of an aqueous extract of ragweed and report that the delayed absorption of the mixture results in a greater tolerance of large doses and so in better relief. It is of particular value for extremely sensitive patients. Meantime, Hansel [74] lays stress on the good results from coseasonal intracutaneous treatment of hay fever. He begins with tiny doses of dilute material and then for further injections increases the strength rather than the quantity. Seldom does he use material stronger than a dilution of 1 : 1,000.

Hay fever can occur in animals. At the 1940 meeting of the Association for the Study of Allergy, Wittich [75] exhibited moving pictures of a

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69. Castex, M. R.; Molfino, J. F., and Ruiz Moreno, G.: Primera contribución al estudio de la flora alergógena de la República Argentina; Parthenium Hysterophorus, Bol. Acad. nac. de med. de Buenos Aires, 1940, p. 91. Castex, M. R.; Ruiz Moreno, G., and Solari, M. A.: Segunda contribución al estudio de la flora alergógena de la República Argentina; polen aéreo en la región de Bahia Blanca, Prensa méd. argent. **27**:2399, 1940.

70. Walker, H., and Carron, R. F.: Contribución al estudio de la polinosis en la República Argentina: nueva planta alergogena; el Celtistala, Día méd. (ed. espec. no. 6), 1940, p. 140.

71. Pratt, H. N.; Colmes, A.; Fromer, J.; Green, J. E.; Chafee, F. H., and Clapp, W. B.: Pollen and Mold Survey of Southeastern New England—1940, New England J. Med. **225**:533, 1941.

72. Naterman, H. L.: The Treatment of Hay Fever by Injections of Suspended Pollen Tannate, J. Allergy **12**:378, 1941.

73. Spain, W. C.; Fuchs, A. M., and Straum, M. B.: A Slowly Absorbed Gelatin-Pollen Extract for the Treatment of Hay Fever, J. Allergy **12**:365, 1941.

74. Hansel, F. K.: Coseasonal Intracutaneous Treatment of Hay Fever, J. Allergy **12**:457, 1941.

75. Wittich, F. W.: Spontaneous Allergy (Atopy) in the Lower Animal: Seasonal Hay Fever (Fall Type) in a Dog, J. Allergy **12**:247, 1941.

fox terrier which had all the symptoms of hay fever, as well as positive cutaneous reactions. Furthermore, excessive treatment resulted in a typical general reaction, which was relieved by epinephrine.

Molds.—These organisms need further study. Successful treatment of hay fever depends partly on the technic of dosage, but probably more on the specificity of the material used. In one group of ragweed-sensitive patients the results are satisfactory and easily obtained, but in another group treatment of the same sort, based on cutaneous reactions of much the same character, gives results which are not so good. It is the study of molds which suggests that these small organisms may complicate the picture and that, whereas late hay fever, for example, is due chiefly to ragweed, molds may play a part in its causation. Until recently the discrepancy between positive cutaneous reactions to molds and proof of clinical sensitiveness was rather striking, but now Pennington [76] describes a number of cases in which provocative tests made by applying the mold spores or their extracts directly to the nasal mucous membranes produced symptoms at once. She finds a considerable specificity: The provocative test may give a positive reaction for one mold but not for another. Meantime, Pennington [77] has made a mold survey for Nashville, Tenn., and found that Alternaria is most common. Pratt,[78] too, found that Alternaria causes the most reactions and that numerous crossed reactions occur among various species of the genus Alternaria. Specificity is not of a high degree. Chobot, Dundy and Schaffer [79] found that 27 per cent of 244 patients gave positive cutaneous reactions to Alternaria and that many of them reacted to other molds as well. Ophthalmic tests and nasal tests with the dry spores gave positive reactions in about one-half the cases, but in only a few instances was it possible to culture Alternaria from plates exposed in the patients' homes. Harris [80] subjected 22 patients skin sensitive to Alternaria to a "mold room" test, the air being sprayed with about 1 Gm. of Alternaria spores per 700 cubic feet (20 cubic meters), which were kept circulating by fans. Of 12 patients with typical histories of sensitivity to molds, asthma or rhinitis developed in 8 within ten to sixty minutes. Ten other patients with similar cutaneous reactions but without typical histories tolerated the mold room for an hour with no symptoms except

76. Pennington, E. S.: A Study of Clinical Sensitivity to Air-Borne Molds, J. Allergy **20**:388, 1941.

77. Pennington, E. S.: A Study of the Incidence of Air-Borne Molds and of Skin Sensitivity to Molds, South. M. J. **33**:931, 1940.

78. Pratt, H. N.: Species Specificity of Alternaria in Asthma and Hay Fever, J. Allergy **12**:431, 1941.

79. Chobot, R.; Dundy, H., and Schaffer, N.: Relationship of Mold Reactions to Clinical Symptoms, J. Allergy **12**:46, 1940.

80. Harris, L. H.: Experimental Reproduction of Respiratory Mold Allergy, J. Allergy **12**:279, 1941.

in 1 case. When later the same patients were tested by asking them to inhale a small quantity of the mold powder from a flat toothpick held before the nostril, the results were quite the same as those obtained by the elaborate mold room method.

Waldbott and Ascher [81] describe rust and smut as major causes of allergic conditions of the respiratory tract. Schonwald [82] reports that the isolated spores of molds make a better antigen than does the extract of the whole felt from the surface of a broth culture. In the case of patients sensitive to flour mill dusts, Wittich [83] finds that the smuts which contaminate the grain are important factors in causing the symptoms. He, too, emphasizes the importance of careful study to find the precise cause of trouble, stating that if the dust and its extract are selected properly, hyposensitization is successful in 85 per cent of cases.

Vasomotor Rhinitis.—This term indicates a chronic form of hay fever-like symptom. Wittich [84] found 2 patients sensitive to the Mexican bean weevil, which caused trouble while they were working with peas and beans. A man employed in a spice factory had chronic vasomotor rhinitis because of paprika, according to Gelfand.[85] More important is the paper by Sternberg and Sorrell,[86] in which they present an outline list of some industries in which occupational asthma or vasomotor rhinitis is initiated. It is a useful compilation. Hansel [87] emphasizes once more the importance of staining specimens of the nasal and bronchial secretions to disclose eosinophile cells. On the other hand, Gillies [88] expresses surprise at the frequent presence of eosinophils in nasal polyps of patients who do not display evidence of allergy.

ASTHMA

The theme in the first few paragraphs of this review was determined in part by the increasing number of papers dealing with asthma from causes other than allergy. Prickman and Moersch [89] describe the cases

81. Waldbott, G. L., and Ascher, M. S.: Rust and Smut, Major Causes of Respiratory Allergy, Ann. Int. Med. **14**:215, 1940.

82. Schonwald, P.: Fungus Allergies, Northwest Med. **40**:17, 1941.

83. Wittich, F. W.: The Nature of Various Mill Dust Allergens, Journal-Lancet **60**:418, 1940.

84. Wittich, F. W.: Allergic Rhinitis and Asthma Due to Sensitization to the Mexican Bean Weevil (Zabrotes Subfasciatus Boh.), J. Allergy **12**:42, 1940.

85. Gelfand, H. H.: Vasomotor Rhinitis and Asthma Due to Paprika: Case Report, J. Allergy **12**:312, 1941.

86. Sternberg, L., and Sorrell, A. H.: Occupational Asthma and Vasomotor Rhinitis: An Outline of Some Common Industries Where These Symptoms Are Initiated, New York State J. Med. **41**:1649, 1941.

87. Hansel, F. K.: Allergy of the Upper and Lower Respiratory Tracts in Children, Ann. Otol., Rhin. & Laryng. **49**:579, 1940.

88. Gillies, A. D.: The Histology of Nasal Polypi, M. J. Australia **2**:149, 1940.

89. Prickman, L. E., and Moersch, H. J.: Bronchostenosis Complicating Allergic and Infectious Asthma, Ann. Int. Med. **14**:387, 1940.

of several patients who had asthma but who also had bronchostenosis, with local areas of collapse behind the obstruction. Bronchoscopy did much for them. A technic for studying the bronchi applied by Greenfield [90] is interesting. After the instillation of iodized poppyseed oil he measured the changes in caliber of certain bronchi during inspiration and expiration and found that in certain cases the changes in size were greater than normal whereas in other cases, of the "wet" type of bronchiectasis, the caliber remained the same in expiration as it was when the lung was fully distended. Chapman and Smith [91] made a similar study of iodized poppyseed oil shadows and present an interesting statistical analysis of observations on normal and on abnormal bronchi.

D'Abreu [92] observed through a bronchoscope the formation during an attack of asthma of the same fibrinous plugs which have been described before and which are so characteristic. Pratt [93] also reports finding them, at the autopsy of a child who died of asthma. Autopsies on patients who died of asthma are also described by Barla-Szabó [94] and by Cruciani and associates.[95] Craige [96] describes the pathologic observations on 7 women who died of asthma. Six of them exhibited bronchial plugs; all had many eosinophile cells in the bronchial wall, with thickening of the basement membrane and an increase in the number and size of the bronchial glands.

Loeffler's syndrome is a pneumonic infiltration, transitory in type and always associated with marked eosinophilia. It is not always accompanied by severe clinical illness. Cases are described by Santos [97] and by Freund and Samuelson.[98] Tuberculosis is usually the alternative diagnosis, but the differentiation is important. On the other hand, tuberculosis may in itself give rise to asthma, according to Urbach and

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90. Greenfield, J.: Bronchial Calibre Changes in Bronchiectasis, J. Clin. Investigation **19**:723, 1940.

91. Chapman, J., and Smith, H. D.: Diameters of Normal and Abnormal Bronchi: A Statistical Study, Am. Rev. Tuberc. **43**:504, 1941.

92. d'Abreu, A. L.: Asthmatic Attack Studied Through the Bronchoscope, Lancet **2**:421, 1940.

93. Pratt, H. N.: The Pathologic Physiology of Bronchial Asthma in Children, New England J. Med. **223**:626, 1940.

94. Barla-Szabó, L.: Pathologic Changes in Lungs of Persons Dying During Asthmatic Attack, Orvosi hetil. **84**:622, 1940.

95. Cruciani, A.; Etchemaite, P., and Gavlin, A.: Autopsia de una asmática muerta en crísis, Prensa méd. argent. **28**:247, 1941.

96. Craige, B., Jr.: Fatal Bronchial Asthma: Report of Seven Cases, Arch. Int. Med. **67**:399 (Feb.) 1941.

97. Santos, C.: Sindroma de Loeffler; pleuropneumopatía eosinofílica, Rev. méd. latino-am. **25**:508, 1940.

98. Freund, R., and Samuelson, S.: Transitory Infiltration of the Lung with Eosinophilia: Löffler's Syndrome, Arch. Int. Med. **66**:1215 (Dec.) 1940.

Loew,[99] who found 25 instances in a series of 452 asthmatic patients. Neumann[100] points out, however, that exogenic allergens may cause trouble even in the presence of tuberculosis and that the two diseases, pulmonary tuberculosis and asthma, do not by any means exclude each other.

Asthma resulting from the pressure of an extrabronchial tumor is listed in the table. A patient with sarcoidosis whose asthma was promptly relieved after treatment through the bronchoscope has been described by Benedict and Castleman.[101] Emphysema may in itself cause asthma. The literature is reviewed and 32 cases are described by Parker.[102] The difficulty here lies in the relation between the pathologic changes in the air spaces and those in the pulmonary vascular bed. Which of these comes first and leads to the other? Pulmonary arteriosclerosis, or Ayerza's disease, in the early stages is hard to recognize. In the advanced form cyanosis is typical. An interesting case is reported by Mason,[103] in which the patient died of rapid obstruction of the pulmonary arterioles, leading to failure of the right side of the heart. In this case the obstruction was due to emboli of small carcinoma cells arising from a primary tumor of the breast, for which radical mastectomy had been performed nineteen months previously. Similar is the case reported by Balboni,[104] in which multiple thromboses of the smaller pulmonary vessels were found. Incidentally, the author reviews the various pathologic conditions which can produce Ayerza's syndrome.

When emphysema is marked, blebs on the surface of the lung may rupture. This year, Caldwell[105] and Skinner[106] each add a case to the list of previous observations. Harkavy[107] describes a group of 8 patients with interstitial pulmonary infiltration, electrocardiographic changes and

99. Urbach, E., and Loew, A.: Bronchial Asthma and Pulmonary Tuberculosis, Am. Rev. Tuberc. **62**:174, 1940.

100. Neumann, W.: Tuberkulose und Asthma, Wien. klin. Wchnschr. **53**:1021, 1940.

101. Benedict, E. B., and Castleman, B.: Sarcoidosis with Bronchial Involvement, New England J. Med. **224**:186, 1941.

102. Parker, R. L.: Pulmonary Emphysema: A Study of Its Relation to the Heart and Pulmonary Arterial System, Ann. Int. Med. **14**:5, 1940.

103. Mason, D. G.: Subacute Cor Pulmonale, Arch. Int. Med. **66**:1221 (Dec.) 1940.

104. Balboni, V. G.: Multiple Pulmonary Thrombi Associated with Cyanosis and Right-Sided Cardiac Hypertrophy, New England J. Med. **223**:22, 1940.

105. Caldwell, H. W.: Spontaneous Mediastinal Emphysema, J.A.M.A. **116**:301 (Jan. 25) 1941.

106. Skinner, H. J.: Asthma Complicated by Subcutaneous Emphysema in Children, J. Pediat. **18**:117, 1941.

107. Harkavy, J.: Vascular Allergy: Pathogenesis of Bronchial Asthma with Recurrent Pulmonary Infiltration and Eosinophilic Polyserositis, Arch. Int. Med. **67**:709 (April) 1941.

a high degree of eosinophilia. Six of them had a pleural effusion with eosinophils. Periarteritis nodosum was not proved in all the cases, but he considers the patients as having various degrees of a "hyperergic vascular reaction." Incidentally, Thompson and Paddock [108] found that if a drop of fresh blood is sealed under a cover glass with petrolatum and let stand for a week, Charcot-Leyden crystals will form, provided the blood contains many eosinophile cells. The crystals arise from the eosinophils.

Treatment of Asthma.—Unfortunately, there is little new in the treatment of asthma. Epinephrine and ephedrine are essential, and it is good to have a complete study of the nature, the origin and the physiology of epinephrine, as presented by Cori and Welch.[109] In their paper is an instructive table, which compares the chemical formulas of the members of this group of substances. Epinephrine, ephedrine and amphetamine benzedrine sulfate are closely related to each other, as well as to tyrosine and to phenylalanine. Epinephrine in oil is widely used, but not so widely as before. It is a suspension rather than a true solution, and so absorption of the drug is irregular, which leads to unexpected reactions in certain cases. Brown [110] has a good idea. He gives ephedrine by mouth in a special enteric-coated tablet which delays absorption for three or four hours—after bedtime. Amphetamine is more toxic than epinephrine. It has no bronchodilator effect and so is not useful in the treatment of asthma, according to Cameron and Kasanin,[111] who present a pharmacologic study of it. (The chemical formulas in this paper vary somewhat from those of Cori and Welch.)

Theophylline and Its Relatives: These compounds are often useful. Theophylline is a xanthine derivative related to caffeine and to theobromine. It is a diuretic and also a cardiac and cerebral stimulant, but its good effect in cases of status asthmaticus is not yet explained. Brown and Mark [112] review its action. Theophylline with ethylenediamine is being used widely in the treatment of asthma, not only in pills given by mouth in cases of simple asthma but, more important, as an effective emergency treatment for severe attacks in doses of 3¾ grains (240 mg.) dissolved in 10 cc. of water and injected intravenously. Young and

108. Thompson, J. H., and Paddock, F. K.: The Significance of Charcot-Leyden Crystals, New England J. Med. **223**:23, 1940.

109. Cori, C. F., and Welch, A. deM.: Glandular Physiology and Therapy: The Adrenal Medulla, J.A.M.A. **116**:2590 (June 7) 1941.

110. Brown, E. A.: A New Type of Medication to Be Used in Bronchial Asthma and Other Allergic Conditions, New England J. Med. **223**:843, 1940.

111. Cameron, W. M., and Kasanin, J.: A Pharmacologic and Clinical Revaluation of Amphetamine (Benzedrine) Sulfate, New England J. Med. **224**:544, 1941.

112. Brown, C. L., and Mark, G. E., Jr.: The Therapeutics of Theophylline and Theophylline Derivatives, Tr. Am. Therap. Soc. **39**:68, 1941.

Gilbert [113] report that the drug can inhibit both histamine shock and anaphylactic shock in guinea pigs.

Theophylline monoethanolamine (theamin, Lilly) deserves more attention. In an excellent article Lamson and Bacon [114] describe its use in the treatment of asthma. There is evidence that caffeine can relax bronchial spasm as well as stimulate the respiratory center. "Not a few patients have discovered that a cup of hot black coffee may afford relief from asthma although sympathomimetic drugs may have failed." It was Prof. Paul Hanzlik who suggested that theophylline would be better than caffeine. It is effective when given by mouth. Lamson and Bacon lay great stress on dosage. In the case of ephedrine doses smaller than ⅜ grain (25 mg.) are often quite as good as doses twice as large. This is important, but in the case of theophylline monoethanolamine it is more important. More patients are relieved by doses of 1 or 2 grains (65 to 130 mg.) than by quantities as large as 5 or 6 grains (300 to 400 mg.), although sometimes these larger amounts are necessary. Untoward effects are not serious; most common are nausea and vomiting. What these authors emphasize is timely. All drugs should be used properly. In allergy, particularly, in which drugs are used for relief and not for treatment of the cause, results would be better if the drugs were used in quantities not larger than the smallest effective dose, regardless of the amount which the commercial pills contain. Half the pill may work as well.

Intratracheal Injection of Iodized Oil: This procedure was recommended a few years ago, but now the end result becomes apparent. Seibold [115] writes that in 641 cases the mortality rate increased 500 per cent in the first year of the use of iodized oil as a therapeutic measure. It may be justifiable to give oil once or twice for diagnostic purposes, but it should never be used for therapy.

Expectorants: These are discussed in an interesting paper by Holinger, Basch and Poncher.[116] They studied the p_H and the viscosity of sputum and found that these properties varied in different conditions. They were interested more in cases than in drugs. Oxygen is an anti-expectorant. It dries the secretions and increases their viscosity. Carbon

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113. Young, R. H., and Gilbert, R. P.: The Use of Theophylline with Ethylenediamine (Aminophyllin) for the Control of Bronchial Spasm, J. Allergy **12**:235, 1941.

114. Lamson, R. W., and Bacon, L. C.: Theophylline Mono-Ethanolamine: A Critical Study of Its Use in the Treatment of Asthma and Other Allergies, J.A.M.A. **116**:915 (March 8) 1941.

115. Seibold, G. J.: An Evaluation of Iodized Oil as a Therapeutic Agent in the Treatment of Bronchial Asthma, Texas State J. Med. **36**:386, 1940.

116. Holinger, P.; Basch, F. P., and Poncher, H. G.: The Influence of Expectorants and Gases on Sputum and the Mucous Membranes of the Tracheobronchial Tree, J.A.M.A. **117**:675 (Aug. 30) 1941.

dioxide, on the other hand, is an excellent expectorant, and the authors suggest that it be used more often. Whether the patient can tolerate concentrations of carbon dioxide up to the 5 or 10 per cent which the authors advise remains to be seen. The best effect apparently is obtained by combining oxygen with carbon dioxide and water (either as steam or as vapor from a mechanical humidifier). If cardiac function is good, carbon dioxide can be given even in the presence of cyanosis and severe dyspnea and may accomplish much.

URTICARIA AND SERUM DISEASE

Urticaria.—There are two good papers this year which treat of urticaria in its broad aspects and in its relation to internal medicine. One is by Winkenwerder,[117] of Johns Hopkins University School of Medicine; the other by Baird,[118] of Boston. The literature on urticaria solaris is reviewed by Arnold.[119] The treatment of urticaria is always difficult, and histamine has been advised in the effort to increase the systemic tolerance to histamine. Alexander and Elliott [120] gave histamine in 49 cases, with satisfactory results in 19 cases. The method was to give a small intravenous dose of histamine, well diluted with saline solution and sufficient in quantity to produce slight flushing. When it works, the results are dramatic. Kahn and Grothaus [121] treated chronic urticaria on a basis of allergy, making cutaneous tests with strong extracts and then eliminating the corresponding foods. Cereals and fruits seemed to be the chief offenders, and the results were good in 17 of 18 cases. Stout and Kositchek [122] treated 58 patients by injecting a hypertonic solution of dextrose intravenously; 43 of them obtained satisfactory relief. Ten of these were patients with serum sickness, and one wonders whether the disease would not have terminated soon even without treatment. Angioneurotic edema of the hereditary type may be a separate disease entity, and I believe that the term Quincke's edema

117. Winkenwerder, W. L.: The Relationship of Urticaria and Angioneurotic Oedema to Internal Medicine, Pennsylvania M. J. **43**:1073, 1940.

118. Baird, P. C., Jr.: Medical Progress: Etiology and Treatment of Urticaria; Diagnosis; Prevention and Treatment of Poison-Ivy Dermatitis, New England J. Med. **224**:649, 1941.

119. Arnold, H. L., Jr.: Urticaria Solaris: Review of Literature and Report of a Case, Arch. Dermat. & Syph. **43**:607 (April) 1941.

120. Alexander, H. L., and Elliott, R. W.: Treatment of Chronic Urticaria with Intravenous Injections of Histamine, J.A.M.A. **114**:522 (Feb. 10) 1940.

121. Kahn, I. S., and Grothaus, E. M.: Treatment of Chronic Urticaria, Based on Successful Outcome of Seventeen out of Eighteen Cases, South. M. J. **33**:1086, 1940.

122. Stout, O. M., and Kositchek, R. J.: Parenteral Use of Hypertonic Dextrose for Relief of Pruritus and of Serum Sickness, Arch. Dermat. & Syph. **42**:802 (Nov.) 1940.

should be used to designate the condition, which occurs in families and which is not infrequently of serious prognostic import. Fineman [123] discusses the subject and describes 2 cases, in 1 of which the patient died of edema of the glottis.

Serum Disease.—This condition is closely related. Each year there are reports of serious, sometimes fatal, reactions after the injection of various therapeutic substances. For example, Ferguson [124] describes the case of a small boy who was given tetanus antitoxin because of deep abrasions received in an automobile accident. The antitoxin was given at 3:05 p. m., and in fifteen minutes severe dyspnea developed suddenly. The chest was in full inspiration. Artificial respiration was begun, and epinephrine was injected. In twenty-five minutes a large wheal developed at the site of the injection of the antitoxin, and the whole flexor surface of the forearm became red and edematous. More epinephrine was given, together with a diethylamine compound. His pulse improved for a few moments, but in fifteen minutes he was weaker again, and intravenous administration of a 5 per cent solution of dextrose was started. In forty-five minutes large quantities of frothy, blood-stained fluid began to pour from the lungs. The intravenous injection was stopped, and the patient's head was lowered to facilitate drainage. Oxygen was given, and the patient improved, but suddenly, at 5:30 p. m., two hours and a half after the antitoxin was given, he stopped breathing and could not be revived. The diagnosis at autopsy was "serum reaction, with pulmonary edema."

Newell and McVea [125] reviewed 500 cases in which tetanus antitoxin was given and found that in 11.8 per cent some type of reaction developed, usually a local reaction, which appeared within a few hours. Frank serum sickness occurred in only 4.4 per cent of cases. Wadsworth and Brown [126] observed a boy aged 11 who was given horse serum and in whom in twenty-four hours a high temperature developed, with rash, cyanosis and a rapid pulse—a severe reaction.

What is the real incidence of reactions like this? So far, there are no good figures, chiefly because the circumstances are so different in each case. When the dose is large, serum disease is more frequent. The condition is rarely fatal. When an acute, sometimes fatal, reaction occurs, it begins in a few minutes or, more rarely, in a few hours. Some-

123. Fineman, A. H.: Hereditary Angioneurotic Edema, Ann. Int. Med. **14**:5, 1940.

124. Ferguson, R.: Fatal Serum Reaction, Canad. M. A. J. **43**:469, 1940.

125. Newell, C. E., and McVea, C.: The Prophylactic Use of Tetanus Antitoxin: The Analysis of Five Hundred Cases, South. M. J. **33**:962, 1940.

126. Wadsworth, G. H., and Brown, C. H.: Serum Reaction Complicated by Acute Carditis, J. Pediat. **17**:801, 1940.

times there is a history of previous treatment with the same material: The patient was actively sensitized. In most cases there is no such history and no particular reason to suspect trouble. Meantime, one reads that hundreds, perhaps thousands, of injections of serum have been given with no particular reaction. Perhaps, however, in these large series the physicians were aware of the danger and so were careful to ask a few crucial questions. Is there evidence of clinical allergy in the patient or in his family? Has he ever had reactions or peculiar episodes which were unexplained? As Rutstein, of the New York State Board of Health, and his associates [127] state: ". . . The incidence of immediate serum reactions in the patients with asthmatic histories was greater (45.5 per cent) than in those without such histories (29.6 per cent)." Reactions are always specific. Even if the patient does give a history of hay fever or of food allergy, it does not mean that serum is dangerous of necessity. The history is simply a warning of the danger and of the importance of taking all possible precautions—and a cutaneous test is easy to make.

Tetanus Toxoid.—This is being used on a large scale. The armies of France, Britain and Italy have used it routinely, and, according to Rouquies,[128] no case of tetanus among the immunized soldiers has been reported. Reactions, however, sometimes occur, particularly with the second dose. Cunningham,[129] Whittingham [130] and Parish and Oakley [131] report cases of anaphylactic shock following its use. The incidence seems to be about 1 per cent.

ALLERGY OF THE SKIN

"Eczema," or "dermatitis" of the atopic type, with its characteristic distribution on the face, the neck and the cubital and popliteal spaces, with its cutaneous reactions of the immediate urticarial type and with a blood serum which can transfer the sensitiveness to a normal person, is quite comparable to hay fever and asthma. Little new is said about it this year, though Hill [132] discusses the problem well.

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127. Rutstein, D. D.; Rogers, E. S., and McCaffrey, I.: The Significance of a History of Asthma with Reference to Serotherapy, New England J. Med. **225**: 368, 1941.

128. Rouquies, L.: Le tétanos la vaccination et la séro-vaccination, Presse méd. **48**:497, 1940.

129. Cunningham, A. A.: Anaphylaxis After Injection of Tetanus Toxoid, Brit. M. J. **1**:522, 1940.

130. Whittingham, H. E.: Anaphylaxis Following the Administration of Tetanus Toxoid, Brit. M. J. **1**:292, 1940.

131. Parish, H. G., and Oakley, C. L.: Anaphylaxis After Injection of Tetanus Toxoid, Brit. M. J. **1**:294, 1940.

132. Hill, L. W.: Eczema in Infants and Young Children, New England J. Med. **223**:624, 1940.

Contact dermatitis, in which the sensitiveness is localized to certain portions of the skin and in which trouble comes not through the blood stream underneath but through direct contact on the surface, is more dramatic, since discovery of the cause of trouble leads usually to a perfect cure. There are numerous reports. Bauer [133] describes the case of a physician with localized dermatitis caused by his elastiglass wrist watch strap. Hollander [134] observed 3 patients with dermatitis of the face due to contact with nail lacquer. In two other papers, he [135] reports, first, on a dermatitis due to the rubber sponge which a woman used as a powder puff—patch tests with the face powder itself were quite negative—and, second, on a dermatitis due to the stain on the handle of a kitchen knife. Brown and Brown [136] had a patient who was sensitive to mangos, and Schwartz and Warren [137] had one who was sensitive to copperweed. Walters and Stern [138] incriminate the dextrin used in a cigaret factory as an adhesive for tax stamps. Guy and Jacob [139] found that girls employed in capping whisky bottles had a dermititis from parachlorometacresol, the shipping fluid in which the caps were preserved. After the caps were washed no new cases of the dermatitis appeared. In a canning factory, Vickers [140] found that 32 of 205 workers showed positive reactions in patch tests to the carrot extract which caused their dermatitis. Another occupational disease was arsenic dermatitis, found in tobacco workers. Barksdale [141] was able to trace the trouble to the insecticide used in destroying plant parasites. Stewart's [142] patient had

133. Bauer, W. W.: Delayed Appearance of Reaction to Elastiglass Wrist Watch Strap, J. A. M. A. **116**:404 (Feb. 1) 1941.

134. Hollander, L.: Nail Lacquer Dermatitis, J. A. M. A. **115**:1714 (Nov. 16) 1940.

135. Hollander, L.: Dermatitis Due to a Face Powder Conveyor, J. A. M. A. **115**:2271 (Dec. 28) 1940; Dermatitis Due to a Stain on the Wooden Handle of a Kitchen Knife, Arch. Dermat. & Syph. **43**:381 (Feb.) 1941.

136. Brown, A., and Brown, F. R.: Mango Dermatitis, J. Allergy **12**:310, 1941.

137. Schwartz, L., and Warren, L. H.: Dermatitis Caused by Contact with Copperweed (Oxytenia Acerosa), J. Allergy **12**:63, 1940.

138. Walters, J. D., and Stern, E. C.: Dermatitis Due to Dextrins Used as an Adhesive on Tax Stamps, J. A. M. A. **116**:1518 (April 5) 1941.

139. Guy, W. H., and Jacob, F. M.: Dermatitis Due to Parachlormetacresol, J. A. M. A. **116**:2258 (May 17) 1941.

140. Vickers, H. R.: The Carrot as a Cause of Dermatitis, Brit. J. Dermat. **53**:52, 1941.

141. Barksdale, E. E.: Cutaneous Manifestation from Tobacco, J. A. M. A. **115**:672 (Aug. 31) 1940.

142. Stewart, C. D.: Dermatitis Due to Mesquite Wood, Arch. Dermat. & Syph. **42**:937 (Nov.) 1940.

trouble from mesquite sawdust. Jordon, Dolce and Osborne [143] emphasize the role of soaps in causing dermatitis on the hands of housewives.

Poison ivy sensitivity is of greater practical importance and has now been studied more extensively. Shelmire [144] reviews the botanic classification. The small climbing vines are called Toxicodendron radicans, and the same plants may also grow into small shrubs. A variety, however, has large oaklike leaves and is called Toxicodendron quercifolium. In California a third variety is called Toxicodendron diversilobum. Poison sumac, Toxicodendron vernix, is obviously different from the other plants. In each case, the milky sap, when applied in crude form to the skin of a normal person, is irritating enough to cause necrosis and eschars. Shelmire finds that patients sensitive to any one of these plants are sensitive also to the others. He made experiments in destroying the poison and found that neither by drying in air, nor by soaking in water nor by boiling could he remove the active principle. Clothing once contaminated remains poisonous. In discussion of this paper, Sulzberger makes a pertinent remark, "If this is so, why doesn't every one have poison ivy dermatitis all the time?" It is a good question, to be answered presumably by the fact that not all people are as exquisitely sensitive as the subjects which Shelmire used to test the activity of his preparations. In another paper, Shelmire [145] gives a useful technic for extracting the resins of various plants. Mature plants are gathered, dried on paper in a darkened room, broken or ground and packed in a jar. Ether is added and allowed to stand for twenty-four hours, after which the ether extract is allowed to evaporate and the residue is taken up in various volumes of acetone. This residue is then preserved in small cork-stoppered bottles. The extract is applied by touching the moistened end of the cork to the unbroken skin of the patient, and the acetone is allowed to evaporate. The sites mark themselves by their green color, and no dressing or cover is necessary. Sixty tests can be made in five minutes. If the patient is sensitive, a localized area of dermatitis will appear at the test site in two or three days. Patch tests with poison ivy give positive results in many patients. Greenberg and Mallozzi [146] observed 119 positive reactions in a group of 278 men. Of those who reacted posi-

143. Jordon, J. W.; Dolce, F. A., and Osborne, E. D.: Dermatitis of Hands in Housewives: Role of Soaps in Its Etiology and Methods for Its Prevention (Especially by Use of Soap Substitutes), J. A. M. A. **115**:1001 (Sept. 21) 1940.

144. Shelmire, B.: The Poison Ivy Plant and Its Oleoresin, J. Invest. Dermat. **4**:337, 1941.

145. Shelmire, B.: Contact Dermatitis from Vegetation, South M. J. **33**:337, 1940.

146. Greenberg, S., and Mallozzi, E.: Experiments in Poison Ivy Sensitivity: Effects of Specific Injections on the Level of Sensitivity to Quantitative Patch Tests and on Clinical Susceptibility, Arch. Dermat. & Syph. **42**:290 (Aug.) 1940.

tively, clinical dermatitis developed in 39 per cent on exposure, but of those whose reactions to patch tests were negative, only 9 per cent had trouble. Reuter and White [147] have studied the interval between exposure and the onset of symptoms. A small patch about 2 cm. square was cut from a fresh poison ivy leaf and rubbed on the skin, and then a dry dressing was applied. Among the 23 subjects studied the incubation period varied from one to eighteen days. The duration of the lesion varied from two to twenty-one days.

Specific treatment of poison ivy sensitiveness remains unsatisfactory. At the meeting of the Association for the Study of Allergy in June 1940 Shelmire [148] gave a fascinating account of a nurse who was exquisitely sensitive to poison ivy. Treatment by mouth was begun with 1 drop of ivy oleoresin in corn oil in a dilution of 1:200. In three months the nurse could take 15 drops of the oleoresin in a dilution of 1:50. Patch tests were positive, though the reactions were less intense than those which preceded the therapy. When they had healed, the dose was increased rapidly to 60 drops of oleoresin in a dilution of 1:25. Four days later rather severe pruritus ani developed, the healed patch test sites flared and a red, blotchy, generalized rash appeared. (Silvers [149] reports the case of a woman who chewed poison ivy leaves. A severe eruption developed in her mouth and about the anus, but there were no gastrointestinal symptoms.) More treatment made the rash worse but did not cause any changes in blood pressure, in the results of urinalysis or in blood counts. When in two weeks the rash had faded a further patch test with the oleoresin in a dilution of 1:100 resulted in erythema, with slight swelling: the nurse could actually pick poison ivy and crush the leaves without trouble. Later the oral administration was resumed and continued until she was taking each day more than 25 cc. of the oleoresin in corn oil in a dilution of 1:25 (55 capsules containing 15 drops each). Patch tests produced a slight erythema, as before, but actual exposure to poison ivy remained harmless.

OTHER MANIFESTATIONS OF ALLERGY

The wide variety of other allergic reactions was mentioned earlier in this review. They provide evidence that one kind of tissue may be more sensitive than another. Here are some further examples.

147. Reuter, R. J., and White, S. F.: Susceptibility to and Latency of Poison-Ivy Dermatitis, New England J. Med. **224**:460, 1941.

148. Shelmire, B.: Cutaneous and Systemic Reaction Observed During Oral Poison Ivy Therapy, J. Allergy **12**:252, 1941.

149. Silvers, S. H.: Stomatitis Venenata and Dermatitis of the Anal Orifice from Chewing Poison Ivy Leaves, J. A. M. A. **116**:2257 (May 17) 1941.

Perera [150] observed a patient who had sensitiveness of the conjunctivas to nupercaine. Miller [151] recognized that the lesions of the lips (cheilitis) of a young woman were due to the vapors of the oil of cinnamon in bubble gum. A patch test and, later, a fume test were both positive. Cohen and Brodsky [152] gave 0.50 cc. of tincture of digitalis to a young woman, and within one-half hour generalized erythema, with urticaria, developed. The second and third doses, given some days later, resulted in a similar violent general reaction.

Dermatitis medicamentosa is always interesting, and the subject is reviewed by Brunsting [153] and also by Burckhardt.[154]

Blood dyscrasias caused by allergy should be recognized, for their proper diagnosis may be of crucial importance. Thomas and Forsythe,[155] at the Cleveland Clinic, found that in 10 of 64 patients purpura haemorrhagica depended on allergy. In each case one or more allergic manifestations were present. On the other hand, treatment on the basis of allergy did not bring relief in all cases. Loveman and Simon [156] report the case of a patient in whom erythema nodosum was clinically dependent on her sensitiveness to sulfanilamide. However, all methods of testing her with the drug gave negative results. Patch tests and intradermal tests with tissue extract from a nodule and with blood serum were all negative both on normal and on previously sensitized areas.

Allergic reactions to insulin, to extracts of liver, pituitary gland and pancreas or to estrogens and other endocrine substances are not uncommon, and a large literature has developed concerning this. It is reviewed in an excellent study by Harten and Walzer.[157] Their paper contains 169 references. To their list of cases a few more recently reported ones can be added. Criep [158] observed 2 patients sensitive to pancreatic tissue

150. Perera, C. A.: Ocular Sensitivity to Nupercaine, Arch. Ophth. **24**:344 (Aug.) 1940.

151. Miller, J.: Cheilitis from Sensitivity to Oil of Cinnamon Present in Bubble Gum, J. A. M. A. **116**:131 (Jan. 11) 1941.

152. Cohen, R. V., and Brodsky, M. L.: Allergy to Digitalis, J. Allergy **12**:69, 1940.

153. Brunsting, L. A.: Dermatitis Medicamentosa, Minnesota Med. **24**:169, 1941.

154. Burckhardt, W.: Allergic Toxicodermatoses: I. Eczema; II. Drug Exanthemata; III. Urticaria; IV. Purpura; V. Erythemas, Dermatologica **79**:175, 1939.

155. Thomas, J. W., and Forsythe, J. R.: Allergy in Relation to Purpura, J. Lab. & Clin. Med. **26**:1105, 1941.

156. Loveman, A. B., and Simon, F.: Erythema Nodosum from Sulfanilamide, J. Allergy **12**:28, 1940.

157. Harten, M., and Walzer, M.: Annual Review: Allergy to Insulin, Liver, Pituitary, Pancreas, Estrogens, Enzymes, and Similar Substances, J. Allergy **12**: 72, 1940.

158. Criep, L. H.: Allergy to Pancreatic Tissue Extract, with Report of Two Cases, J. Allergy **12**:154, 1941.

extract. They gave positive cutaneous reactions to the material, and it was possible to detect antibodies in their serum, since passive transfer to a normal person was successful. Andrews [159] reports the case of a patient who was sensitive to liver extract and then was desensitized by daily injections of increasing size. Wechsler, Farmer and Urban [160] report the case in which a patient's reaction to insulin simulated an attack of coronary occlusion but when positive cutaneous reactions were given to many brands of insulin, including crystalline insulin, the diagnosis became clearer and the prognosis better. Reactions to insulin in patients with diabetes are not common. Yasuna [161] reviewed the case records of 3,323 diabetic patients admitted to the Boston City Hospital since 1929 but did not find any cases of generalized insulin sensitiveness. Also he studied the literature but could find a total of only 12 cases, and it is interesting that in 8 of these there was evidence of allergy other than the sensitivity to insulin.

Allergic gastritis is mentioned by Hansen,[162] with proper comment on the importance of a family history and of other evidences of allergy in the same patient. Recurrent vomiting in children may be of allergic origin, according to Fries and Jennings.[163] Ménière's disease has been mentioned earlier in connection with the experience of Horton [61] that histamine given intravenously may be a successful method of treatment. Bowen [164] observed 14 patients who suffered from allergic conjunctivitis. The family history was positive; about one half of them had hay fever, the others being sensitive to cosmetics, drugs or foods. He points out wisely that vernal catarrh is a form of contact dermatitis, a local sensitiveness of the conjunctivas, and is so not likely to give positive cutaneous reactions comparable to those obtained in cases of atopic allergy. Cormia [165] expresses the belief that food sensitivity can aggravate acne vulgaris and states that he helped 70 per cent of his patients to obtain relief by changing their diets.

The list of papers mentioned here is long, but it is in no way complete. As in previous reviews, much selection has been necessary. Many important articles, as well as several whole topics, have been omitted. To include them all takes space and is not essential. The object has

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159. Andrews, C. T.: Allergic Reaction to Liver Extract, Lancet **1**:664, 1941.

160. Wechsler, H. F.; Farmer, L., and Urban, J. A.: A Case of Insulin Allergy Simulating Coronary Occlusion, J. Lab. & Clin. Med. **26**:1090, 1941.

161. Yasuna, E.: Generalized Allergic Reactions to Insulin: Review of the Literature, with Report of a Case, J. Allergy **12**:295, 1941.

162. Hansen, K.: Gastritis allergica, Deutsche med. Wchnschr. **67**:197, 1941.

163. Fries, J. H., and Jennings, K. G.: Recurrent Vomiting in Children, J. Pediat. **17**:458, 1940.

164. Bowen, R.: Allergic Conjunctivitis, South. M. J. **34**:184, 1941.

165. Cormia, F. E.: Food Sensitivity as a Factor in the Etiology of Acne Vulgaris, J. Allergy **12**:34, 1940.

been to call attention to those papers which seemed to throw light on fundamental principles and not to present long lists of isolated observations. The review may be of some value to those whose primary interest is allergy, but I hope that it will draw the attention of physicians who work chiefly in other fields. I hope that they will at least turn the pages to see the number of topics which apply to their own practice.

Allergy is a practical problem, and its manifestations are encountered in any and all fields of medicine. The ophthalmologist sees vernal catarrh; nasal polyps worry the rhinologist; nerve lesions complicate serum reactions, and intestinal urticaria is confused with appendicitis. Bladder allergy is described. The practicing physician sees allergic reactions in one form or another almost every day. Antitetanus serum is given to large numbers of persons on slight provocation. Then all physicians give drugs. Each year come new drugs, with complicated formulas and with actions which are known and good, but with side effects which are less known and which are not so good. If the physician will only think of allergy, he will have made a gain in his understanding of the case at hand. If, then, he knows somethings of the principles of allergy, he will appreciate its limitations and will distinguish what allergy can do from what it cannot do. He will know that to be really valid a diagnosis based on allergy must also be based on common sense.

263 Beacon Street.

News and Comment

Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation.—Thirty-five grants were made by the trustees of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation during 1941, one being a continued annual grant.

In the eighteen years of its existence the foundation has made four hundred and twenty-nine grants, which have been distributed to investigators in Arabia, Argentina, Austria, Belgium, Brazil, Canada, Chile, China, Czechoslovakia, Denmark, Egypt, Estonia, Finland, France, Germany, Great Britain, Greece, Hungary, India, Iraq, Italy, Latvia, Lebanon, Netherlands, North Africa, Norway, Palestine, Peru, Poland, Portugal, Rumania, South Africa, Sweden, Switzerland, Syria, Venezuela, Yugoslavia and the United States.

In their first statement regarding the purposes for which the fund would be used, the trustees expressed themselves as follows:

> "1. For the present, researches will be favored that are directed towards the solution of problems in medicine and surgery or in branches of science bearing on medicine and surgery.
>
> "2. As a rule, preference will be given to researches on a single problem or on closely allied problems; it is hoped that investigators in this and in other countries may be found, whose work on similar or related problems may be assisted so that more rapid progress may be made possible.
>
> "3. Grants may be used for the purchase of apparatus and supplies that are needed for special investigations, and for the payment of unusual expenses incident to such investigations, including technical assistance, but not for providing apparatus or materials which are ordinarily a part of laboratory equipment. Stipends for the support of investigators will be granted only under exceptional circumstances."

In the past few years the policy outlined in paragraph 2 has been neglected. During the present great need for funds, grants will be given in the sciences closely related to medicine without reference to special fields. The maximum size of grants will usually be less than $500.

Requests for grants to be held during the year 1942-1943 must be in the hands of the executive committee before April 1942. Letters asking for aid must state definitely the qualifications of the investigator, give an accurate description of the research, the size of the grant requested and the specific use of the money to be expended. In their requests for aid, applicants should state whether or not they have approached other foundations for financial assistance. It is highly desirable to include letters of recommendation from the directors of the departments in which the work is to be done. Only requests complying with the conditions cited will be considered.

Requests should be sent to Dr. Joseph C. Aub, Collis P. Huntington Memorial Hospital, 695 Huntington Avenue, Boston, Mass., U. S. A.

Mississippi Valley Medical Society 1942 Essay Contest.—Each year the Mississippi Valley Medical Society offers a cash prize of $100, a gold medal and a certificate of award for the best unpublished essay on any subject of general

medical interest (including medical economics) and practical value to the general practitioner of medicine. Certficates of merit may also be granted to physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents of the United States. Five copies of each contribution, which should not exceed 5,000 words and which should be typewritten in English, should be in the hands of the secretary, Dr. Harold Swanberg, 209 W. C. U. Building, Quincy, Ill., not later than May 1, 1942. Further details may be secured from Dr. Swanberg.

Book Reviews

Exercises in Electrocardiographic Interpretation. By Louis N. Katz, M.D., Assistant Professor of Physiology, University of Chicago. Price, $5. Pp. 222, with 189 electrocardiograms. Philadelphia: Lea and Febiger, 1941.

Experiments in methods of clinical teaching are always interesting. In 1906 Dr. Richard C. Cabot, of Boston, published a volume "Case Teaching in Medicine." It was an effort to apply to medicine the case-teaching method used successfully in the Harvard Law School. The teacher could obtain a key list of the correct diagnosis for each case reported, so that he was always sure to be right, and the students could struggle over the Cabot records to their hearts' content, acquiring considerable agility in that form of mental gymnastics which has to do with the clinical management of paper patients.

This particular method of teaching met with a certain degree of favor for a time and was applied to other fields—pediatrics, neurology and obstetrics. On the whole, however, while the clinical-pathologic conference has survived from it, the patient in vivo has seemed better to study than the patient in vitro, and clinical clerkships have proved infinitely more educational than even the most careful analysis of case histories.

"Exercises in Electrocardiographic Interpretation" is an outcropping of a tendency toward reviving this old teaching method and applying it to a new field. The book begins with a 17 page discussion of how to analyze, describe and interpret electrocardiograms. This is followed by 90 short case reports, each accompanied by beautifully reproduced electrocardiographic tracings pertinent to the case described, intelligently and skilfully interpreted. At the end three appendixes deal with ways of filing and classifying electrocardiograms in a systematic and approved fashion.

Such a method of teaching electrocardiographic interpretation may well prove helpful to many groups of physicians or students. This reviewer confesses to remembering with much pleasure a game of penny ante which for a time was fashionable in the hospital in which he resided. A group of interns would assemble, and each man would put up a penny for each tracing which the cardiologist would supply for the evening's entertainment. The intern who interpreted correctly any single tracing which the others missed would win all money placed on that particular tracing, but if half or more of the group interpreted the same tracing correctly, no pennies would change hands, such an occurrence being the foundation for building up a small jack pot. It was a good game while it lasted and besides being fun to play evolved into a useful method of instruction. Perhaps this book will help to resurrect that particular indoor sport.

Essentials of Electrocardiography. By Richard Ashman, Ph.D., and Edgar Hull, M.D. Price, $5. Pp. 373, with 122 figures. New York: The Macmillan Company, 1941.

The first edition of "Essentials of Electrocardiography" appeared four years ago. As the authors point out, since that time there have been numerous accretions to the knowledge of cardiography; consequently, it has been necessary to rewrite a goodly part of the book and to increase its length. As a matter of fact, it might be said almost to be a new book, in contradistinction to a second edition in which a few minor changes have been made.

The book consists of 15 chapters, together with an appendix and an excellent bibliography, the latter some 20 pages long. The same general form is followed as was used in the first edition. The usual introductory chapters on the fundamentals of the electrocardiogram occupy a considerable portion of the book.

The reader, being familiarized with the basic principles and with the normal electrocardiogram, is then introduced to the abnormal deviations that appear as a result of heart disease, anemia, a metabolic disturbance, a toxic state, infection or any one of the host of conditions which may produce alterations from the norm.

The reviewer has nothing but praise for this book. The senior author is one of the pioneers in the study of the physiology of the heart by means of the electrocardiogram. The junior author is a skilled clinician and is apparently responsible for the clinical features, which are so well presented. The format is excellent; the subject matter is printed on a high grade, semiglossy paper which reproduces well the expected innumerable electrocardiograms. The book can be recommended highly to the tyro in this field, to the clinician who dabbles in electrocardiography and to the skilled electrocardiographer who may wish at times to consult a magnificent reference book and to obtain the opinion of others who are skilled in this field.

An X-Ray Atlas of Silicosis. By Arthur J. Amor, M.D. (Lond.), M.Sc. (Wales), Honorary Physician, Clydach Memorial Hospital; Medical Officer, Mond Nickel Co., Ltd., Swansea, Wales. With translation of the legends into French by Robert E. Horne, M.A. (Wales), Medical Secretary, Mond Nickel Co., Ltd., Swansea, Wales. Price, $8, cloth. Pp. 206, with 72 illustrations. Baltimore: Williams & Wilkins Company, 1941.

Since so many of the general textbooks of medicine devote so little space to silicosis, this atlas should occupy a prominent place in the newer concept and the diagnosis of this industrial disease. The author has had many years of experience among the industrial workers of South Wales, including the medical supervision of a large colliery. He has kept accurate and careful records of thousands of cases and has verified the diagnoses by postmortem examinations and by the statutory certificates of the Silicosis and Asbestosis Medical Board.

The first portion of the book consists of 5 chapters devoted to the etiology, pathology, roentgenology, clinical manifestations and prognosis of silicosis. A brief discussion of the roentgen anatomy of the normal chest is included in this section. The division of silicosis into three clinical stages, as described by Sutherland and Bryson, is employed. Stages 1 and 2 each are subdivided further into three subtypes. The association of tuberculosis and silicosis is considered fully.

The atlas contains 72 excellent full page reproductions of roentgenograms which illustrate the various stages and types of silicosis as well as the most frequent complication, tuberculosis. In several instances, reproductions of photographs and roentgenograms of the lung made post mortem are included. On the page opposite each illustration are legends in English and French describing the occupation and a brief medical history of the patient, the roentgenographic findings and the diagnosis of his condition. A short bibliography is included.

The Microbe's Challenge. By Frederick Eberson. Price, $3.50. Pp. 354. Lancaster, Pa.: The Jaques Cattell Press, 1941.

Under this intriguing title and covered by a dramatic dust wrapper is a really excellent book for the layman on bacteriology and infectious disease. An extract from the publisher's letter gives perhaps better than the reviewer can an outline of its substance:

"The book deals with one of the brightest chapters in medical history, telling a story of war against disease and the vaunted conquests of man over his invisible germ enemies. Against a historical background of past and present medical discoveries and their application is shown how microbes wage war against man with counter-attacks of their own, ingenious and diabolically human. The novelty of the theme is in its presentation from the point of view of a microbal 'struggle for existence' as they seek food, shelter and continuous survival at the expense of human and animal 'hosts,' leaving disease in their wake.

"The author shows that in this changing world, microbes have been changing too, deriving their power from new characteristics in the body of a victim, or while passing from one to another. It tells of epidemics and what science does to prevent outbreaks of disease; how new diseases are created which later turn out to be new forms of the old. Man the conqueror finds himself outflanked by a smart adversary in the exciting chapters on the mysteries of infantile paralysis, yellow fever, malaria, influenza, plague and the various viruses—carriers of disease."

The author in the effort to catch the reader's fancy has titled his chapters with all sorts of vivid legends, such as "Virus Riddles," "Jekyll and Hyde Types," etc., but when one comes to "The Taming of the Flu" one feels (as P. G. Wodehouse would say) that this is a shade over the odds.

The Principal Nervous Pathways. By A. T. Rasmussen, Ph.D., Professor of Neurology, Department of Anatomy, University of Minnesota Medical School. Second edition. Price, $2.50. Pp. IX + 73, with 28 illustrations. New York: The Macmillan Company, 1941.

The first edition of this book appeared in 1932. For some reason it was not much noticed by the ordinary clinician, though it was reviewed favorably by such special journals in the field of neurology as the *Archives of Neurology and Psychiatry* (**27**:1513 [June] 1932) and the *Journal of Nervous and Mental Disease* (**76**:94 [July] 1932).

Now that internists wish to have at least a bowing acquaintance with the central nervous system this recent edition is a godsend, for it is as simple a book on so complicated a subject as there can be, pretending to be no more than a finely reproduced graphic presentation of the chief nervous pathways.

The second edition is the same size as the first, but the author has made such alterations in text and illustrations as to bring out changes which have become reasonably well established as new knowledge in the past decade. Thus here is a means of teaching pictorially to any interested students the essentials of modern neuroanatomy.

The author admits that some of the cuts may seem to be overburdened with legends. On the other hand, most readers will agree that this is better than to be forced to hunt up some other sketch in order to find the name of a structure that is shown but not labeled.

The book is a useful tool for students or for the harassed internist who wishes to learn the precise anatomic sites of many physical changes which are readily demonstrable at the bedside. It deserves great success.

Essentials of Endocrinology. By Arthur Grollman, Ph.D., M.D., Associate Professor of Pharmacology and Experimental Therapeutics (formerly Associate Professor of Physiology and Instructor in Chemistry) in the Johns Hopkins University School of Medicine. Cloth. Price, $6. Pp. 480, with illustrations and index. Philadelphia: J. B. Lippincott Company, 1941.

Should the reviewer be asked to choose a single volume book about the hormones for the student or the practitioner of medicine, he would unhesitatingly recommend this one. The author has presented a "critical evaluation of all important aspects of the subject." To quote further from the preface, "Clinical endocrinology is frequently befuddled by accepting unproved assumptions as basic facts and building upon the insecure foundations, thus established, a maze of fanciful and ill-founded conjectures. When reduced to its experimentally established facts, clinical endocrinology can be placed on a scientifically sound basis. Since so much of endocrinology is based on observations in human disease, it is impossible to dissociate experimental from clinical endocrinology."

The exposition is sane and cautious as well as orderly. In each instance the fundamental facts of gross, comparative and microscopic anatomy, embryology, physiology and pathology on which the experimental and the clinical studies are based are stated and discussed. No conclusion is drawn unless it is fully supported

both by clinical and by experimental evidence. The illustrations and charts are excellent and clear. A carefully selected but adequate bibliography is inserted at the end of each chapter.

Therapeutisches Taschenbuch. By P. Mühlens, M.D., Director of the Institute for Tropical Disease, Hamburg, Germany. Second edition. Price, 1.50 marks. Pp. 76, with 20 illustrations. Leipzig: Georg Thieme, 1941.

The first edition of this booklet came out in 1939. *The Journal of the American Medical Association* acknowledged its appearance (**114**:917 [March 9] 1940) and seemed somewhat scandalized by its short skirts. *The Journal* termed the little volume too brief and sketchy and suggested that here was an attempt at oversimplification of a serious subject. Evidently this hussy had more appeal than was strictly commendable in the society of good medical books, however, for the author says that the first edition of 2,000 copies was gobbled up within a year of its printing.

The second edition has now been published, and no doubt the book will once again captivate many readers with its brusqueness of style and its abbreviated costume. It pretends to do no more than give a bird's-eye view of the most common tropical diseases and their treatment. The serious student of tropical medicine can properly object to the book's superficiality. Many readers, however, will like to know of its existence and that here can be found an extremely condensed account of the kind of medical problem with which an expert in the field of tropical medicine is now forced to contend.

Shock Treatment in Psychiatry: A Manual. By L. Jessner, M.D., and V. Gerard Ryan, M.D. Price, $3.50. Pp. XV + 149. New York: Grune and Stratton, Inc., 1941.

This short monograph reviews in a workman-like manner the use of insulin, metrazol and electricity as agents for inducing convulsing shocks in psychiatric therapy. These three agents and the technics of their usage are evaluated critically and in language that any one can understand.

Each chapter is built on the same lines. A short historical account is followed by a description of technical procedures, a statement of the indications and the contraindications for using the agent under discussion and, finally, a general summary of the results to be expected. As a concluding chapter, the author supplies a bibliography of 353 references culled from several thousand titles.

The book begins with an introduction by Dr. Harry Solomon. He says that it is an excellent handbook; and so it appears to be, useful not only to the psychiatrist but to the internist, who nowadays, perforce, is supposed to be somewhat informed about the problems of shock therapy, and to the inquiring medical student. On the whole, this unassuming small volume deserves high praise.

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CALCIFICATION OF THE PANCREAS

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Deposition of calcium salts in the pancreatic tissue is an uncommon pathologic finding. Clinical diagnosis of the condition is even more unusual, and few case histories have been reported. Beling,[1] in a thorough survey of the literature, found 12 cases in which diffuse calcification of the pancreas was thought to be present, and to these he added an instance of his own. We have reviewed the original articles and cannot agree that cases 1 and 3 cited by him have sufficient evidence to be considered examples of the syndrome under discussion.

According to Mayo,[2] two types of calcium deposits within the pancreas have been described. The first, "true stones," are concretions of calcium salts lying free in the ducts. These may be single or multiple and usually lie in the larger ducts. The second variety he termed "false stones," actual calcifications of the parenchyma of the pancreas. It is the latter condition which will be considered. True stones, which sometimes occur in conjunction with the calcareous precipitations in the gland, are apparently not essential to the latter condition.

Including the case presented by Beling but excluding cases 1 and 3 in the résumé compiled by him, there are, we believe, 11 recorded instances in which clinical, roentgenologic and pathologic data are sufficient to warrant the diagnosis of calcification of the pancreas. For a more extensive review of the literature, the article of Beling should be consulted.

We wish to record 3 examples of this condition observed by one of us and also give a brief summary of a case which may fit into this category.

From the Subdepartment of Neurology of the Johns Hopkins University School of Medicine and the Department of Medicine of the Baltimore City Hospitals.

1. Beling, C. A.: Calcification of the Pancreas, Am. J. Digest. Dis. **7**:231, 1940.

2. Mayo, J. G.: Pancreatic Calculi, Proc. Staff Meet., Mayo Clin. **11**:456, 1936.

REPORT OF CASES

CASE 1.—P. D., a white man aged 35, came to the Johns Hopkins Hospital complaining of abdominal pain of six weeks' duration. The family history was noncontributory. As a child he had had mumps, complicated by orchitis on the left side. Three years before his entrance into the hospital an appendectomy had been performed. For a long period he had been a heavy drinker, and the year following the operation, while he was undergoing a cure for alcoholism at a local hospital, glycosuria was discovered. The diabetes was controlled by diet, but after leaving the hospital he had returned to his former habit and sugar reappeared in the urine. During rehospitalization, diabetes was controlled by a daily dose of 45 units of insulin. At the time of discharge the urine was kept sugar free by diet alone.

Six weeks before admission to the Johns Hopkins Hospital the patient experienced a dull ache in the epigastrium, most severe in the afternoon and evening. Ingestion of food increased the discomfort, and sodium bicarbonate did not afford relief. Ten days previous to entrance a sudden attack of vomiting occurred, and the vomitus contained all he had eaten for the past two days. He recognized undigested food particles, but neither blood nor pus was noted. He was admitted again to a local hospital, where the epigastric pain became sharper and more severe but did not radiate. Ingestion of alcohol brought rapid relief. For two days no solid food was eaten because of the increased pain following meals. No history of jaundice, hematemesis, diarrhea, chills or fever could be obtained. Laboratory examination yielded the following salient data: a blood sugar value of 212 mg. per hundred cubic centimeters, glycosuria and radiopaque material in the upper part of the abdomen. The patient was referred to Dr. John T. Howard, of the Johns Hopkins Hospital, for further study.

Physical examination on admission to this hospital revealed nothing abnormal except the abdominal symptoms. The abdomen was symmetric and soft, with a well healed incision in the right lower quadrant. The edge of the liver could be felt 2 cm. below the right costal margin and was rounded and tender on palpation. Mild tenderness was elicited on deep pressure in the right upper quadrant near the midline of the abdomen.

Laboratory examination added the following information: red cell count, 5,310,000 and white cell count, 21,750 per cubic millimeter; hemoglobin content, 16.2 Gm. per hundred cubic centimeters, and corrected sedimentation rate 26 mm. at the end of one hour. A differential count of the white cells showed 6 per cent juvenile granulocytes, 74 per cent segmented neutrophils, 17 per cent lymphocytes and 3 per cent monocytes. Platelets were normal both in size and in quantity. The Wassermann reaction of the blood was negative. Determinations of the nonprotein nitrogen, sugar, calcium and phosphorus of the blood yielded values of 38, 210, 9.5 and 4.4 mg., respectively, per hundred cubic centimeters. The bromsulphalein test of hepatic function revealed less than 5 per cent retention. The urine was clear, with an acid reaction, a specific gravity of 1.032 and a positive reaction for sugar but with no albumin, acetone or cellular structures. Stools were of normal consistency but had a strongly positive guaiac reaction. They were also positive for fats and fatty acids, as demonstrated by the use of sudan III.

A dextrose tolerance test showed a high rise and slow fall of the blood sugar level (fig. 1), and specimens of urine consistently contained sugar. A normal flow of bile was found on duodenal drainage, but on microscopic examination of the fluid flocculi and many pus cells were seen. Tests for pancreatic enzyme activity failed to show any active trypsin or diastase. However, a twenty-four hour specimen of urine contained more than 1,200 units of diastase.

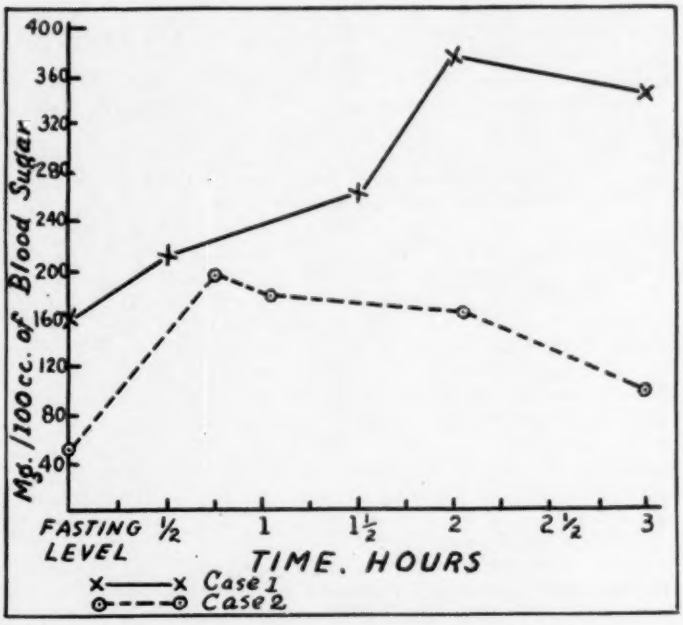

Fig. 1.—Dextrose tolerance curves in cases 1 and 2.

Fig. 2 (case 1).—Calcified particles outlining the pancreas.

Roentgen ray examinations revealed a normal heart and aorta, clear lungs, a normally functioning gallbladder in which no stones could be demonstrated and diffuse calcification of the entire pancreas (fig. 2).

With routine hospital care, the abdominal discomfort was almost entirely relieved. The diabetes was regulated, and the patient was discharged, having only to follow a prescribed diet to prevent glycosuria.

Four days after discharge the patient had a sudden, severe attack of pain in the upper portion of the abdomen, which lasted for several hours and was followed by frequent attacks of vague epigastric discomfort. He was readmitted five days later, at which time the physical examination disclosed nothing abnormal. The urine again contained sugar. The diabetes was quickly controlled by a 2,200 calory diet and 23 units of insulin daily. Ten days later an exploratory laparotomy was performed by Dr. W. F. Rienhoff Jr., who found the pancreas sausage shaped, freely movable, hard and dense, with the surrounding blood vessels small. The midportion of the gland was incised, and a small calculus fell out. The parenchyma was white and glistening, and no blood appeared on the cut surfaces. The ducts were probed in both directions and found patent. Disease of the biliary or the gastrointestinal tract was not evident. A portion of the pancreas was removed for microscopic study.

According to the report, the pancreatic tissue was scarce. There were a few acini, surrounded by large amounts of connective tissue, a few atrophic and scarred islands of Langerhans and several dilated ducts. Neither free calculi nor actual calcification was demonstrable.

After an uneventful postoperative course, the patient was discharged; his diabetes was under control, but the epigastric discomfort remained.

A third admission occurred five months later. Since the last discharge there had been occasional attacks of abdominal pain, which were relieved by morphine. The pain radiated to the right and left costal margins and to the lower left part of the chest. The results of physical examination were again essentially negative. Stools no longer showed free fat, and duodenal drainage yielded dark bile, which was normal microscopically. Free fat could be demonstrated in the duodenal contents by the sudan III stain. Active trypsin and diastase were absent. The diabetes was controlled by diet and daily administration of 20 units of protamine insulin.

Since the last admission, the patient has been seen frequently by his local physician. The abdominal pain continues but has diminished. Since his recent marriage his health is much improved.[3]

Case 2.—A Negress aged 35 was admitted to the Baltimore City Hospitals with a complaint of pain in the right side of her abdomen. The family history was noncontributory. She had had the usual childhood diseases and had not undergone any operations. Three pregnancies had all terminated in miscarriage. Four years before admission she had been thrown from a motorcycle and had sustained fractures of the skull, ribs and right arm. For many years she has been a heavy consumer of beer and strong liquor. During the past year her weight had fallen from her average of 112 to 80 pounds (50.8 to 36.3 Kg.). Chronic constipation had been troublesome for many years.

The patient stated that for the past six months she had had periods of ill health characterized by pain in the lower right portion of the chest. Vomiting had been frequently associated with these attacks of pain. The pain and vomiting bore no relation either to the type of food eaten or to the time of ingestion.

3. Crawford, R. H.: Personal communication to the authors.

For the past two months there had been an almost constant aching pain which included the entire anterior aspect of the right side of the chest and radiated through the scapula. Five days before admission the pain became severe and localized beneath the right costal margin.

Physical examination disclosed a small but well developed Negress who was not in acute distress. The skin showed evidence of loss in weight but was otherwise normal. Several observers mentioned slight tenderness in the right upper quadrant of the abdomen. However, no viscera or abdominal masses were palpated. Nothing further of importance was detected.

Laboratory procedures, which included complete studies of the blood, urine, stool and cerebrospinal fluid, disclosed nothing abnormal. The Wassermann reactions of the blood and spinal fluid were negative. Analysis of a fasting specimen of gastric contents showed 8 degrees of free and 12 degrees of combined hydrochloric acid. Visualization of the gallbladder, both after oral and after intravenous administration of radiopaque dye, showed a normally functioning organ with no evidence of stones. Visualization of the gastrointestinal tract demonstrated an irregularity in the prepyloric region of the lesser curvature of the stomach and failure of the duodenal cap to fill. This was interpreted as spasm; so the procedure was repeated, and it was decided that the upper part of the gastrointestinal tract was normal. Some abnormal calcification was present in the upper portion of the abdomen, but this was not commented on.

Soon after admission the pain disappeared and the appetite returned. A low grade fever, never satisfactorily explained, persisted throughout the stay in the hospital. Eructation was frequent after meals, but there was no complaint of discomfort. On discharge, a diagnosis of possible cholecystitis was made.

After remaining well for approximately eighteen months, she experienced, on May 27, 1938, severe, sharp substernal pain, which subsided after a short rest in bed. Discomfort returned the following day, and the patient remained in bed until her second admission to the Baltimore City Hospitals, on June 3. Three days after the onset of abdominal pain, intermittent attacks of vomiting appeared, and both pain and vomiting persisted until her arrival at the hospital. On one occasion blood was noted in the vomitus.

On admission, the temperature, pulse and respiration were normal; the blood pressure was 110 systolic and 80 diastolic, and the results of physical examination were entirely negative. Laboratory studies, however, showed many changes since the previous admission. Examination of the urine and blood revealed nothing abnormal. The reaction to 0.1 cc. of old tuberculin in a dilution of 1 : 1,000 was positive. The Wassermann reaction of the blood was positive, but that of the cerebrospinal fluid was negative. Blood sugar estimations showed 98 and 87 mg. per hundred cubic centimeters (fasting specimens). The concentrations of calcium and phosphate were 8.8 and 4.0 mg., respectively, per hundred cubic centimeters of blood. Analysis of gastric contents during fasting showed no free but 12 degrees of combined hydrochloric acid; after administration of alcohol, 32 degrees free and 18 degrees combined acid, and after injection of histamine, 35 degrees free and 55 degrees combined acid. A dextrose tolerance test gave a curve with a steep rise and a slow fall (fig. 1). Specimens of urine collected during the test showed values for sugar varying from 0.2 to 0.5 mg. per hundred cubic centimeters.

The stools were not grossly abnormal, but fecal material stained with sudan III disclosed a marked increase of fat. There was no amylase in the stools, and

only traces were present in the urine. The tests were repeated one month later, with similar results. Analysis of the duodenal contents, obtained by direct drainage, disclosed 3 units of amylase (normal, 40 units) but no trypsin. These tests were repeated, with the same results.

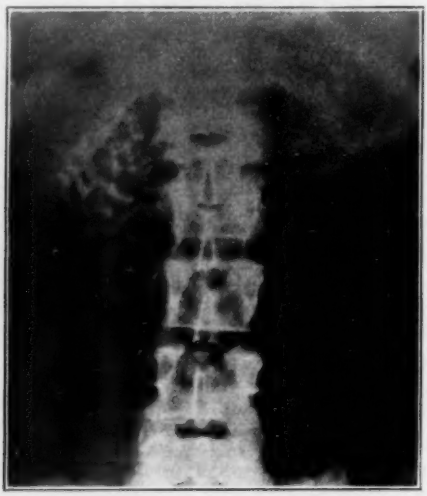

Fig. 3 (case 2).—Calcification in the upper part of the abdomen in the region of the pancreas.

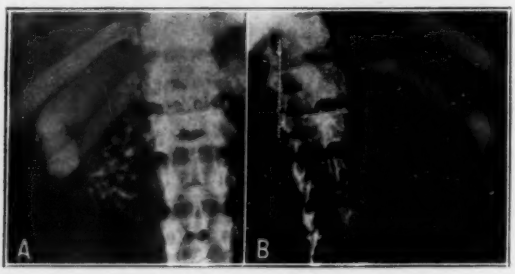

Fig. 4 (case 2).—*A*, anteroposterior view of the calcification in the region of the pancreas shown in relation to the gallbladder, which is filled with radiopaque dye. *B*, lateral view taken at the same time.

Roentgenograms of the chest, gallbladder and gastrointestinal tract were normal. Plain roentgenograms of the abdomen taken at this time showed many radiopaque bodies in the region of the pancreas which were interpreted as calcification of the pancreas (figs. 3 and 4).

The patient's discomfort rapidly disappeared when she was given a high carbohydrate, low fat diet, and she was discharged without further treatment.

CASE 3.—E. B., a Negress aged 17, was admitted to the Baltimore City Hospitals on June 3, 1937 because of polyuria. The family history is of interest because of the prevalence of obesity. The mother weighed 185 pounds (83.9 Kg.) at the age of 18 years, and at the time of admission the patient weighed 246 pounds (111.6 Kg.). A sister aged 13 weighed 186 pounds (84.4 Kg.) and the father 175 pounds (79.4 Kg.). The patient stated that as a child she had had measles, pertussis, diphtheria, scarlet fever and pneumonia. Since then she had suffered from frequent colds and sore throats. Menstruation had started at the age of 11 and had since been irregular. Periods lasted four days, during which considerable flow was present and often severe, cramping pain.

The illness which brought her to the hospital consisted only of moderately severe polyuria (1.5 to 7 liters in twenty-four hours) and a slight loss of weight. The duration of the symptoms was not stated. On admission, the general physical examination revealed nothing abnormal except marked obesity. Urinalysis revealed glycosuria (4 plus) and acetone (1 plus) but no diacetic acid. Determination of the sugar and cholesterol content and of the carbon dioxide–combining power of the blood yielded values of 480 mg. and 150 mg. per hundred cubic centimeters and 47.5 volumes per cent, respectively.

The diabetes was easily regulated and the patient was placed on a daily maintenance dose of 20-0-20 units of regular insulin. While she was in the hospital, the Wassermann reaction of the blood was positive and the basal metabolic rate was + 24 per cent. A roentgenogram of the skull showed no abnormalities of the sella turcica.

After discharge, the patient remained well until July 11, 1939, when she was readmitted because of pyelitis. The infection of the urinary tract subsided quickly under conservative therapy, and the diabetes was again regulated on the same dose of insulin. She was discharged after a short stay.

On August 20 the patient had a sudden chill, followed by malaise and pain in the left side of the abdomen. The next day she became nauseated, vomited and ate nothing. These symptoms persisted; so she did not take her insulin. She was readmitted on August 23.

At the time of examination the patient was not in acute distress. The temperature was 105 F., the pulse rate 130 beats per minute, the respiratory rate 28 per minute and the blood pressure 150 systolic and 80 diastolic. The skin was hot and dry, and there were numerous striae over the upper extremities and abdomen. Moderate spasm and tenderness were present in the left lower quadrant of the abdomen. Otherwise, the physical examination revealed nothing abnormal.

The urine contained albumin (1 plus), sugar (4 plus), acetone (3 plus) and large numbers of white blood cells but no red cells or casts. Examination of the blood showed 3,550,000 red cells and 19,300 white cells per cubic millimeter and 11 Gm. of hemoglobin per hundred cubic centimeters of whole blood. The blood contained 572 mg. of sugar, 26 mg. of nonprotein nitrogen and 26 mg. of cholesterol per hundred cubic centimeters, and the carbon dioxide–combining power was 25 volumes per cent. The serologic reaction of the blood for syphilis was positive, but that of the spinal fluid was negative. No abnormalities of the stools were noted.

The diabetic acidosis was treated vigorously, and sulfanilamide was given for the infection of the urinary tract. Five days later the temperature had fallen to normal, but severe secondary anemia had developed. The sulfanilamide was discontinued, and ammonium mandelate was administered for ten days. By this time the pyelitis had subsided and the diabetes was controlled.

Roentgenograms of the chest, together with intravenous and retrograde pyelograms, failed to reveal any abnormality of the kidneys (fig. 5). Plain roentgenograms of the abdomen revealed many small calcified areas in the epigastrium, which were interpreted as calcification of the pancreas. Unfortunately, no determinations of the activity of the pancreatic enzymes were carried out.

The following case history was discovered in the files of the department of pathology of the Johns Hopkins Hospital. The clinical records

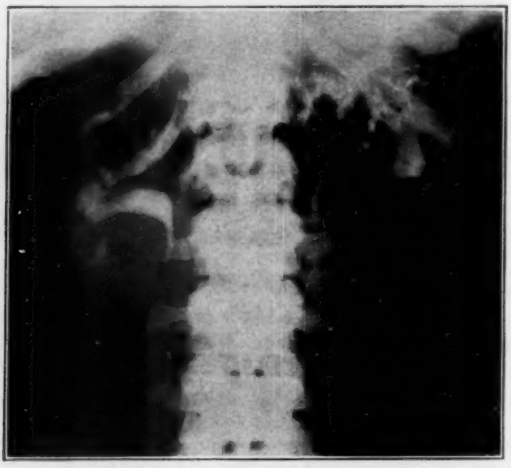

Fig. 5 (case 3).—Calcification in the pancreas shown in relation to the renal pelves, which are demonstrated by means of an intravenous pyelogram.

are scanty, and as the patient died in 1891, roentgenograms and enzyme studies are lacking. The pathologic findings are so typical, however, that we feel certain the case is one of false pancreatic stones.

Case 4.—H. W., a white man aged 43, was admitted to the medical service of the Johns Hopkins Hospital on Oct. 2, 1890 with a complaint of jaundice. The family history was noncontributory. For many years he had been a heavy drinker of strong liquor. Five years before there had been an episode of chills and fever, the duration of which was not stated. An attack of pain in the abdomen, with generalized soreness of the back lasting for several days, had occurred one year before entrance to the hospital. Six months after this there had been frequent attacks of vomiting. About one week before admission epigastric pain, which radiated through to the back, had been experienced, and jaundice had appeared shortly afterward. The latter had already begun to subside, and the abdominal discomfort had disappeared at the time he was seen by physicians at the hospital.

Physical examination revealed nothing abnormal except slight jaundice. No abnormalities of the urine were recorded. The icterus subsided rapidly, and the patient was discharged nine days later, with the diagnosis of catarrhal jaundice.

Pertinent Data in Four Cases of Calcification of the Pancreas

	Case 1	Case 2	Case 3	Case 4
Alcoholism	Chronic	Chronic	Absent	Chronic
Pain				
Duration	6 weeks	5 days; 6 days 18 mo. later	None	5 yr.; 1 yr.; indefinite periods
Location	Epigastrium	Right costal margin	None	Epigastrium
Radiation	Right and left costal margins and lower left chest	Right side of chest anteriorly through to scapula and under sternum	None	Through to back
Increased by taking food	Yes	No	—	—
Increased by type of food	No	No	—	—
Fever	Present for indefinite period	Present for indefinite period	Present for indefinite period	Present for indefinite period
Chills	None	None	Present	Present
Nausea	Present	Present	None	Present
Vomiting	Present	Present	None	Present
Jaundice	None	None	None	Marked 5 years before; slight on admission
Diarrhea	None	?	None	None
Concomitant disease	None	Motorcycle accident	Pyelitis; glandular deficiency (?)	Tuberculosis
Tenderness at the time of physical examination	Epigastrium and right upper quadrant of abdomen	None	None	None
Fever during hospitalization	None	None	None	None
Laboratory findings				
Red cell count	Normal	Normal	Normal	?
White cell count	21,750	Normal	19,300	?
Sedimentation rate	26 mm. per hr.	Normal	?	?
Urine				
Sugar	Present	None	Present	None
Amylase	1,200 units	None	?	?
Other substances	None	None	Acetone, albumin, white cells	None
Stool				
Gross appearance	Normal	Normal	Normal	Normal
Fat (sudan III)	Present	Present	None	?
Trypsin	None	3 units	?	?
Amylase	None	None	?	?
Duodenal drainage				
Amylase	0 units	3 units	?	?
Trypsin	0 units	0 units	?	?
Gallbladder				
Roentgenogram	Normal	Normal	Normal	—
Operation	Normal	—	—	Normal (autopsy)
Appearance of pancreas	Hard, white, scarred	—	—	Hard, white, scarred, calcium deposits
History of loss of weight	None	32 pounds (14.5 Kg.)	Moderate	Marked

He reappeared in the outpatient department on July 29, 1891, with the complaint of cough and dyspnea of one week's duration. Hospitalization was advised, and on entry into the ward his temperature was 102.4 F., his pulse rate 128 per minute

and his respiratory rate 36 per minute. Physical examination showed yellow-tinged scleras. There were signs of a pleural effusion on the right side of the chest, and tubercle bacilli were present in the sputum. The patient rapidly became worse and died five days after admission.

At autopsy a widely dilated pancreatic duct containing many calculi was found. The pancreas was hard and atrophic. When the gland was cut, it imparted a gritty sensation, and deposits of calcium salts were found throughout the parenchyma. No microscopic sections were made. Examination of the lungs disclosed advanced tuberculosis.

COMMENT

Haggard and Kirtly [4] found reports in the literature of 204 cases in which the diagnosis of pancreatic lithiasis had been made. Included with these are the 12 cases of calcification of pancreatic tissue cited by Beling. The incidence of pancreolithiasis observed post mortem is cited by several authors as varying from 1 case in 1,500 to 1 case in 2,500 consecutive autopsies. We have found 5 instances in the first 16,000 autopsies performed at the Johns Hopkins Hospital and none in the first 8,000 done at the Baltimore City Hospitals. Of the 209 cases now recorded, actual calcification of the gland occurred in only 15 (7.1 per cent). In 6 cases the patient was operated on or was examined post mortem, and in every instance true pancreatic stones were found, in addition to the diffuse calcification.

The cause of the calcification is obscure. Mayo expressed the belief that it is due to pancreatitis, in turn produced by chronic disease of the biliary tract. This was refuted by Haggard and Kirtly,[4] who pointed out that gallstones were found in only 9 of the 65 cases of pancreolithiasis in which there was surgical intervention. Biliary calculi were not demonstrated in any of our cases.

A history of signs and symptoms suggestive of cholecystitis is more frequently elicited, being present in 3 of our patients. However, pain severe enough to be interpreted as bilary colic is rare. Should pancreatitis due to infection of the biliary tract precede the calcification, it probably is chronic, slowly progressing cellulitis rather than the severe generalized reaction that follows obstruction of the ampulla of Vater by a biliary calculus, causing an influx of bile into the pancreatic passages.

The length of time between the onset of the postulated pancreatitis and the appearance of the calcification is not known. Patients are often first seen many years after the initiation of symptoms, and when the calcified areas are discovered in roentgenograms, there is no way of determining how long they have been present. There is some evidence that the deposition may be rapid. Chiray, Albot and Bolgert [5] found

4. Haggard, W. D., and Kirtly, J. A.: Pancreatic Calculi, Ann. Surg. **109**:809, 1939.

5. Chiray, M.; Albot, G., and Bolgert, M.: Etude clinique et biologique d'un cas de lithiase généralisée du pancréas, Ann. méd. **38**:348, 1935.

larger quantities of amylase and trypsin in the duodenal contents after one year's observation of their patient. This led them to the conclusion that some regeneration had occurred and that the inflammation had subsided. The pancreas may have sustained a rapid widespread destructive process followed by calcification, but with slow hypertrophy of the surviving tissue. We know that the roentgenogram may show a marked increase in the amount of calcium deposited within eighteen months. In case 2 of our series the first examination was made in January 1937, and only a few calcified areas are apparent in the roentgenograms of the abdomen taken at that time, but in those taken in May 1938 the typical picture of generalized calcification is present. During the interval there were no symptoms of an inflammatory process.

Chronic alcoholism has been mentioned in many cases, and in 3 of our cases the patients were consumers of large quantities of alcohol. However, the patient in case 3 of our series was a young girl who, as far as we know, never drank alcoholic liquors. The role of alcoholism, beyond its apparent frequency, is not known at this time. Certainly, it is not the sole agent in producing the calcium deposits in the pancreas.

Tuberculosis is rarely responsible for calcified areas in the pancreas. Even extensive generalized tuberculosis seldom involves this gland. We consider its presence in case 4 incidental. The same may be said for syphilis and other chronic diseases. One of the acute infectious processes that might be implicated is mumps, which may cause pancreatitis (case 1). Neither in our cases nor in those reported in the literature was there any evidence that the calcium metabolism was abnormal or that a generalized calcium-depositing dyscrasia was present.

The symptomatology is not at all characteristic, the most constant complaint being a poorly localized pain in the upper part of the abdomen. There may be no physical signs. Clinical diagnosis is made on roentgenographic findings alone, as the deposits of the calcium salts are radiopaque. The gland is outlined so clearly that there can be little doubt as to the location of the calcification.

Carbohydrate metabolism is commonly deranged, and Mayo stated that diabetes is frequent. Oser (cited by Chiray and associates) found glycosuria in 24 of 70 cases of pancreatic lithiasis. Glycosuria is mentioned only once in the 11 cases of diffuse calcification of the pancreas reviewed by Beling and checked by us, while an abnormal dextrose tolerance curve was noted in another. Two of our patients had diabetes, while the blood sugar curve of a third was distinctly abnormal (fig. 1). We feel that disturbances of carbohydrate regulation are probably frequent and would be reported more often if dextrose tolerance tests were routine.

Because of our ignorance of the cause and the extensive involvement of the pancreas, no satisfactory method of treatment has been decided on.

Study of the pancreatic enzymes in the urine led to the conclusion that the pancreatic duct was occluded in 1 of our patients, and therefore an exploratory laparotomy was performed, but the main duct was patent. Two patients became asymptomatic under supportive care, and we felt that surgical intervention was not indicated. However, we are by no means satisfied that all types of treatment are unnecessary, and if there is any evidence of a pancreatic abscess or cyst, the lesion should be searched for and treated by the usual surgical methods. A high carbohydrate diet seemed beneficent for 1 of our patients.

Prognosis for the condition is good, but there may be recurrent attacks of pain of varying frequency for many years. Diabetes is not common, but when present is usually mild, shows little tendency to progress in severity and is easily controlled by small amounts of insulin.

SUMMARY

A review of the literature has disclosed accounts of 11 cases of diffuse calcification of the pancreas. Records of 4 additional cases have been presented and the salient facts summarized in a table. The cause, diagnosis, treatment and prognosis have been discussed.

Dr. John T. Howard, of the Johns Hopkins Hospital, and Dr. R. H. Crawford, of Rutherfordton, N. C., permitted us to report case 1.

RELATION OF CALCIUM AND LIPIDS TO ACUTE PANCREATIC NECROSIS

REPORT OF FIFTEEN CASES, IN ONE OF WHICH FAT EMBOLISM OCCURRED

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AND
IRVING A. FIELDS, M.D.
LOS ANGELES

Many facts concerning acute pancreatic necrosis and the accompanying pathophysiologic changes have been well known for years. The yellow-white areas of "fat necrosis" in and around the pancreas were so named by Balser.[1] Langerhans [2] described the action of lipase in splitting neutral fat into fatty acid and glycerin, the latter being absorbed and the fatty acid deposited as needle-like crystals, which combine with calcium to form soaps. Frugoni and Stradiotti [3] stated that 85 per cent of the soaps so formed may be insoluble.

Probably in no other disease is there such sudden demand for calcium, the amount needed depending on the extent of fat necrosis and the subsequent liberation of fatty acids.

We have been unble to find records of further investigations of the rôle of calcium in this disease, either as to the amount combined with the fatty acids in situ or as to the effect of the disease on serum calcium values. The present paper is based on studies of the latter aspect.

Serum lipid determinations were made in some cases, in a search for indications of absorption of neutral fat into the blood (the method used includes determination of fatty acids [4]). It is possible that both neutral fat and fatty acids, such as oleic acid, which is liquid at body temperature, might find their way from the necrotic tissue into the blood stream. Neutral fat is also a solvent for fatty acids, even after they have

This study was aided by a gift from Ethel Mossman Jacobs.

From the Department of Pathology, University of Southern California School of Medicine, and the Laboratory, Los Angeles County Hospital.

1. Balser, W.: Ueber Fettnekrose eine zuweilen todtliche Krankheit des Menschen, Virchows Arch. f. path. Anat. **90**:520, 1882.

2. Langerhans, R.: Ueber multiple Fettgewebsnekrose, Virchows Arch. f. path. Anat. **122**:252, 1890.

3. Frugoni, C., and Stradiotti, G.: Experimenteller Beitrag zur Kenntnis der Fettgewebsnekrose, Berl. klin. Wchnschr. **47**:386, 1910.

4. Boyd, E. M.: The Oxidative Micro-Estimation of Blood Lipids, Am. J. Clin. Path. (Tech. Supp.) **8**:77, 1938.

combined with calcium to form soaps, and thus the acids if absorbed may carry soaps with them.

A few clinical and experimental observations have been made on the lipids in the blood. Wiesel [5] noted fat in the vessels of the liver at necropsy in 3 instances. In 2 of these fat was also present in the renal vessels. The pulmonary vessels were not mentioned. Wijnhausen [6] observed hypercholesterolemia and xanthomatosis of the skin in a 35 year old man with diabetes. At operation chronic pancreatitis and a few areas of fat necrosis were seen. No attacks of typical acute pancreatitis had been noted clinically. Joel [7] studied the blood serum of a young girl in whom acute pancreatic necrosis was observed during a surgical exploration. The serum was grossly milky. The content of cholesterol in the blood was 360 mg. per hundred cubic centimeters, and the amount of neutral fat was estimated at ten times normal, not enough serum being available for actual quantitative determination. Five days later the level of cholesterol was 150 mg. per hundred cubic centimeters, and there was no visible evidence of an increase in serum lipids.

Binet, Brocq and Ungar [8] produced experimental pancreatitis in dogs and observed an increase both in serum cholesterol and in the total lipids. They reported values for serum cholesterol as high as 840 mg. per hundred cubic centimeters and values for total lipids as high as 740 mg. Total lipids were not determined for the dog with a cholesterol value of 840 mg. per hundred cubic centimeters. The authors called attention to a patient with fatal acute pancreatic necrosis for whom the values for total lipids and serum cholesterol were 2,880 and 604 mg. per hundred cubic centimeters, respectively. Brunner [9] reported the results of serum cholesterol and fatty acid determinations for 4 persons with acute pancreatic necrosis. The fatty acids were estimated by Bloor's [10] method, which includes determination of neutral fat. For 1 patient the value for fatty acids was 3,440 mg. per hundred cubic centimeters, the normal being 350 mg. The value for serum cholesterol was 1,040 mg. per hundred cubic centimeters. Fatty acids

5. Wiesel, J.: Ueber Leberveränderungen bei multipler abdomineller Fettgewebsnekrose und Pankreatitis haemorrhagica, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **14**:487, 1905.

6. Wijnhausen, O. J.: Ueber Xanthomatose in einen Falle rezidivierender Pankreatitis, Berl. klin. Wchnschr. **58**:1268, 1921.

7. Joel, E.: Zur Klinik der Lipämie, Ztschr. f. klin. Med. **100**:46, 1924.

8. Binet, L.; Brocq, P., and Ungar, G.: Le syndrome humoral de la pancréatite hemorragique, Presse méd. **37**:848, 1929.

9. Brunner, W.: Beitrag zur pankreatogen en Lipämie, Klin. Wchnschr. **14**:1853, 1935.

10. Bloor, W. R.: The Determination of Small Amounts of Lipid in Blood Plasma, J. Biol. Chem. **77**:53, 1928.

ranged from 368 to 575 mg. and cholesterol from 127 to 264 mg. in the remaining 3 patients.

Our attention was first called to this subject by the condition of a patient who was found to have fat embolism and whose chief symptoms were shock and tetany.

REPORT OF THE CASE OF ACUTE PANCREATIC NECROSIS WITH ASSOCIATED FAT EMBOLISM

F. H. (case 4 of table 2), a 48 year old Mexican woman, entered the Los Angeles County Hospital on Dec. 30, 1939. According to her history, two weeks before entry she had had feverish sensations, nausea and vomiting. Apparently she had recovered, but twenty hours before entry she had had an attack of severe epigastric pain and repeated vomiting. When she was admitted to the hospital, she appeared to be in severe shock; the radial pulse could not be felt, and the oral temperature was 97 F. Typical carpopedal spasm was present, but neither Chvostek's nor Trousseau's sign could be elicited. A mass could be felt in the upper part of the abdomen. The carbon dioxide-combining power of the plasma was 47 volumes per cent. The leukocyte count was 9,100, with 72 per cent neutrophils. The urine contained albumin (2 plus) and many hyaline casts. The level of urinary diastase was within the normal range. The patient's condition rapidly became more serious, and she died nine hours after entry.

Necropsy.—The body was that of a well nourished woman, measuring 160 cm. in length and weighing 63.5 Kg. The feet and hands were flexed. The abdominal cavity contained 200 cc. of cloudy fluid. The tissues about the pancreas, including the mesocolon, were yellowish brown and necrotic. The foramen of Winslow was completely closed. The lesser peritoneal cavity was obliterated by hemorrhage and by swollen, friable, discolored tissue, masses of which broke away readily on manipulation. Necrotic yellow-white areas alternated with islands of hemorrhage throughout the interstitial tissue of the pancreas and in the peripancreatic tissue, extending as far as the upper pole of the left kidney and to the left half of the diaphragm. In the central portion of the pancreas some of the glandular tissue appeared to be fairly normal. The duct of Wirsung contained some clear secretion. Many small veins in and around the pancreas were filled with antemortem clots.

Many adhesions were present around the thickened wall of the gallbladder, which contained about forty black faceted calculi, measuring 5 to 6 mm. in their greatest dimensions. The common duct had a maximum circumference of 1 cm. The common duct and the duct of Wirsung opened side by side in a normal arrangement. The pleural surfaces were smooth. The right lung weighed 380 Gm. The lower lobe was partially collapsed, and dark blue-red areas were seen beneath the pleura. On section blotchy, dark red atelectatic areas interspersed with gray air-containing tissue were seen throughout the lobe. The left lung weighed 360 Gm., and its appearance was similar to that of the right. The consistency of the kidneys was less firm than normal. No gross changes were evident in the heart. The brain was not examined.

The blood was of a peculiar plum color, quite different from that ordinarily seen at autopsy. Blood with a similar color has been observed by one of us (H. A. E.) in a person with severe hyperlipemia (8,400 mg. of lipids per hundred cubic centimeters of blood).

Microscopic Observations.—In the pancreas there was extensive necrosis of the interstitial tissue, ducts and acini at the periphery of the lobules. Many acini and some small ducts appeared to be normal. Wide areas of necrosis extended into the peripancreatic tissue, involving connective tissue, fat and vessels alike, as well as the mucosa of the duodenum and the capsule of the left adrenal gland. Many veins contained thrombi. Finely granular, blue-staining material, which was considered to be calcium soap, was present in many of the necrotic areas. When such an area was stained with scarlet red a large amount of fat was revealed

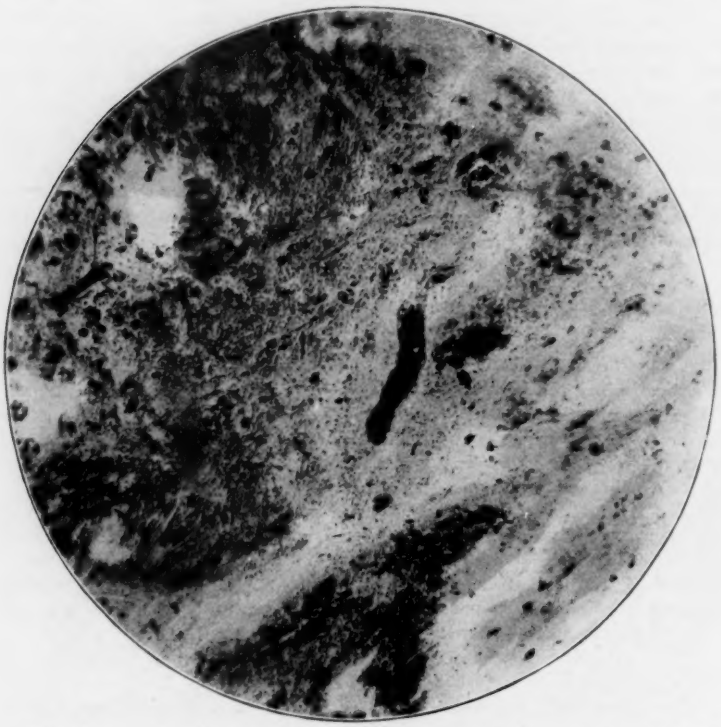

Fig. 1.—A section of the pancreas through an area of necrosis, in which the veins and lymphatic vessels are filled with fat. Scarlet red; × 100.

in the necrotic lesions, much of which was within small veins, venules and lymphatics. Some of these appeared to be completely filled (fig. 1).

The lungs contained areas of atelectasis, and the alveolar capillaries were dilated. The most striking changes were seen in sections stained with scarlet red. Many vessels contained fat droplets of various sizes. Some were fine (about the size of blood platelets), and others were so large that they completely filled the capillaries (fig. 2). Layers of fat droplets adhering to the intima were noted occasionally in the larger vessels (fig. 3). In some areas the vessels contained few fat droplets or none at all.

In sections of the heart stained with scarlet red most of the small veins were found to be completely filled with intensely staining lipids. Some of the capillaries were similarly filled, but the arteries were free of droplets. About one half of the muscle fibers contained fine fat droplets in the cytoplasm in a segmental arrangement typical of fatty degeneration. In sections of renal tissue stained with hematoxylin and eosin little change was observed in the glomeruli and the vessels. The epithelium of the convoluted tubules was finely granular and exhibited changes characteristic of early degeneration. In sections stained with scarlet red many fat droplets were seen in the glomerular capillaries; some

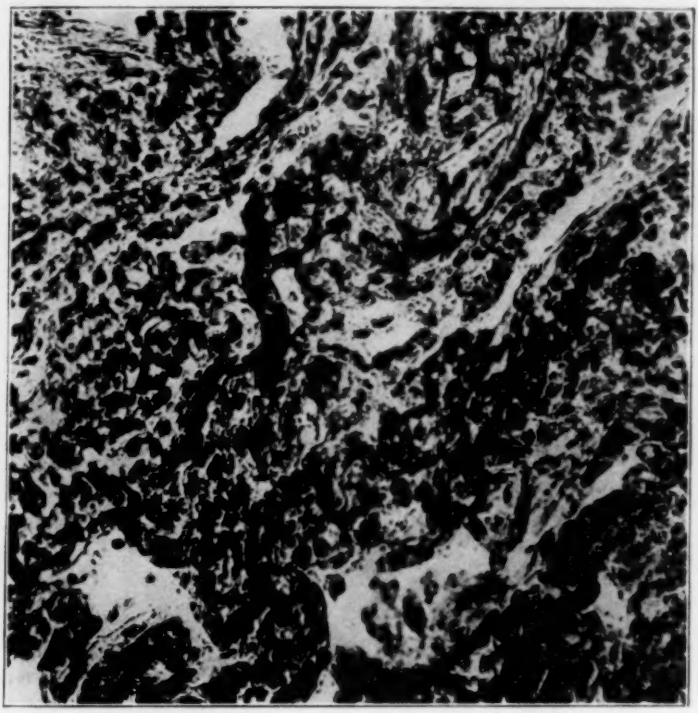

Fig. 2.—Pulmonary capillaries containing fat. × 500.

appeared completely filled. Droplets also occurred in many of the veins. Fine droplets of lipoid material were present in the tubular epithelium.

The cytoplasm of the liver cells contained many large and small vacuoles. No noteworthy changes were visible in the blood vessels. A definite increase of connective tissue and a few mononuclear cells were noted in the periportal spaces. Liver cells stained with scarlet red displayed diffuse fatty changes in the cytoplasm, but little fat was seen in the vascular channels.

The anatomic diagnosis included chronic cholecystitis, cholelithiasis, acute pancreatic necrosis, hyperlipemia, fat embolism and pulmonary atelectasis.

Fat embolism and hyperlipemia were observed in this case. No antemortem determinations of serum calcium were made. Definite fat embolism of the pulmonary and renal vessels was demonstrated. Fat embolism of the cerebral vessels was probably present, but it is questionable whether it caused the tetany. The carbon dioxide–combining power of 47 volumes per cent eliminated alkalosis as the causative factor. The cause of the tetany remains uncertain.

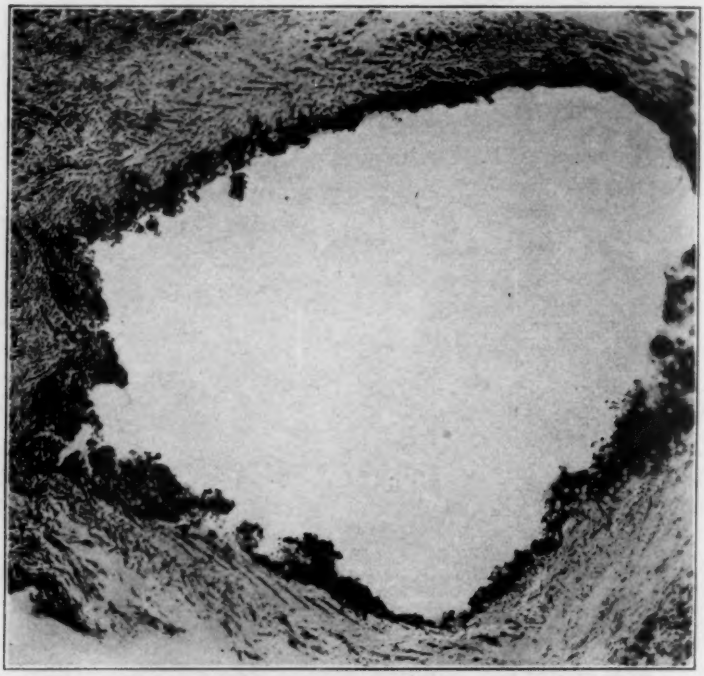

Fig. 3.—Fat droplets adherent to the intima of a pulmonary vessel. × 135.

CALCIUM AND FAT NECROSIS

The possibility of hypocalcemia due to deposition of calcium in the necrotic lesions was also considered as a possible cause of the tetany in the case just reported. The total calcium content of a portion of the pancreas and peripancreatic fat was determined. Unfortunately, only a 2 Gm. specimen was analyzed. This contained 10.5 mg. of calcium, or 525 mg. per hundred grams of tissue. As there was easily 400 Gm. of necrotic tissue, some 2,000 mg. of calcium might be assumed to have been present in combination with fatty acids as soaps. Since only a

2 Gm. sample was analyzed, too much reliance cannot be placed on these figures. However, there can be little doubt that the calcium in the necrotic tissue was enormously increased over the amount in normal tissue.

In a second instance (case 5 of table 2), in which acute pancreatitis followed surgical removal of a calculus from the common duct, the duration of symptoms was less than twenty-four hours and the grossly evident necrosis was confined to the pancreas and the fatty tissue immediately surrounding it. A mass of tissue weighing 210 Gm., taken from these structures yielded 200 mg. of calcium. More recently a third instance (case 6 of table 2) has been studied. The clinical history was not cleancut as to the duration of the disease, but the patient had been ill for seven days. Necropsy revealed obesity and widespread fat necrosis, involving the omentum, the mesentery and the retroperitoneal

TABLE 1.—*The Calcium Content of Lesions in Acute Pancreatic Necrosis, as Compared with That of Pancreatic Tissue*

Case	Calcium Content of Pancreas, Mg. per 100 Gm. of Wet Tissue	Peripancreatic Fatty Tissue, Mg. per 100 Gm. of Wet Tissue	Total Amount of Calcium (Mg.) in Pancreas Plus 2 Kg. of Adjacent Fatty Tissue	
1 (control)	5.6	2.6	Estimated maximum	58
2 (control)	5.3	2.3	Estimated maximum	52
3 (control)	6.0	3.6	Estimated maximum	78
4	525.0	.....	Estimated	1,500
5	.....	.....		200*
6	178.0	152.0		1,732

* In this case the disease was of less than twenty-four hours' duration.

fat. The pancreas and involved fat, with a total weight of 2,250 Gm., was ground three times, and three samples of 5 Gm. each were taken. These samples contained almost identical amounts of calcium, with an average of 3.75 mg., or 75 mg. per hundred grams of tissue. The total amount of calcium was estimated at 1,732 mg. Separate samples of pancreas, peripancreatic fat and omentum were analyzed. These contained 178, 152 and 36 mg. of calcium per hundred grams of tissue, respectively (table 1).

Samples of pancreatic tissue from 2 moderately obese men (cases 1 and 2 of table 2) aged 43 and 68, respectively, and 1 woman (case 3 of table 2) aged 62 were used as controls. They contained 5.6, 5.3 and 6 mg. of calcium per hundred grams of tissue, respectively. Specimens of peripancreatic fat yielded 2.6, 2.3 and 3.6 mg., respectively. As the normal pancreas rarely weighs over 100 Gm., it is evident that in cases of fat necrosis, an excessive amount of calcium collects in the pancreatic tissue.

TETANY

It is assumed that the average human being has a total blood volume of 6,000 cc. and that the total serum calcium is about 600 mg., of which 250 to 300 mg. is diffusible. If only 100 mg. of diffusible calcium is lost more or less rapidly, the concentration of serum calcium may drop to 8.3 mg. per hundred cubic centimeters if the calcium is not replenished from reserves. The extracellular body fluids amount to approximately three times the plasma volume and constitute a reservoir of calcium which is in equilibrium with that in the blood.[11]

Estimates of the total amount of calcium in the extracellular fluids have been made by studies of transudates [12] which revealed an average content of 7.5 mg. per hundred cubic centimeters, or a total of 750 mg. of calcium. This would tend to offset the drop in serum calcium. It may be noted in table 1 that in 1 case (C. L.) the 1,732 mg. of calcium deposited in the necrotic pancreas and surrounding fat was greater than the total normal amount of calcium in the blood and tissue fluids.

Another problem of importance is to determine how quickly the parathyroid glands, acting through solution of parathyroid, may replenish lost serum calcium. In experimental animals twenty to eighteen hours elapses after an injection of parathyroid extract before serum calcium reaches its maximum level.[13] No experimental evidence was found that gave any clue as to how quickly the calcium level would return to normal in an intact animal after a sudden decrease of serum calcium.

Three instances of tetany associated with acute pancreatic necrosis have been reported. Bertelsman [14] operated on a 33 year old white woman who had suppurative cholecystitis and acute pancreatic necrosis. On the second day after operation she had tetanic convulsions. Serum calcium was not determined. Intravenous administration of calcium and solution of parathyroid was followed by the prompt disappearance of tetany. The patient recovered, and a year later no clinical evidence of disturbance in calcium metabolism was apparent. Bertelsman expressed the belief that the tetany was due to the pancreatitis but did not discuss the mechanism.

Cibert and Plauchu [15] noted severe tetany in a man aged 32 in whom acute hemorrhagic pancreatitis was revealed during an exploratory lapa-

11. Gamble, J. L.: Extracellular Fluid, Bull. Johns Hopkins Hosp. **61**:151, 1937.

12. Greene, C. H.; Bollman, J. L.; Keith, M. M., and Wakefield, E. G.: The Distribution of Electrolytes Between Serum and Transudates, J. Biol. Chem. **91**:203, 1931.

13. Collip, J. B.: The Parathyroid Glands, Medicine **5**:1, 1926.

14. Bertelsman, R.: Postoperative Tetanie bei eitriger Cholecystitis und akuter Pankreasnekrose, Zentralbl. f. Chir. **54**:324, 1927.

15. Cibert, J., and Plauchu, M.: Pancréatitite aiguë hémorragique et tétanie, Lyon méd. **152**:587, 1933.

rotomy thirty-nine hours after the onset of illness. The tetany ceased twenty-four hours after operation. They discussed only the possibility of the tetany being due to vomiting, with the resultant loss of chlorides and the accompanying loss of calcium.

Amano and Murata [16] observed tetany in a 29 year old Japanese woman seen on the second day of her illness. The level of serum calcium was 10.3 mg. per hundred cubic centimeters, but nevertheless intravenous administration of calcium was followed by cessation of the tetany. The patient was subjected to an operation. Extensive fat necrosis was found, a cholecystotomy was done and recovery ensued. The authors suggested three possible causes of the tetany: (1) disturbance of the external secretion of the pancreas; (2) disturbance of the internal secretion of the pancreas, and (3) intoxication due to peritonitis.

REPORT OF TWELVE CASES OF ACUTE PANCREATIC NECROSIS

We have studied to date a series of 12 cases in which we are convinced both by clinical findings and by the values for urinary diastase (method of Fabricius and Moeller, cited by Foged [17]) and/or those for blood amylase (method of Somoygi, cited by Elman [18]) that there was evidence of acute pancreatic necrosis. Total serum lipids (not including cholesterol) were determined in 6 of the 12 cases. Brief clinical summaries follow. (The results of the calcium and lipid studies are given in table 2.)

CASE 1.—B. W., a 30 year old white woman, was admitted to the hospital on March 4, 1940 because of severe persistent midepigastric pain of nine hours' duration. Similar attacks lasting about one-half hour had occurred for the past ten days. On admission the patient appeared acutely ill; respirations were shallow, and both upper quadrants of the abdomen were rigid and tender. The temperature was 101 F., the pulse rate 118 per minute and the blood pressure 95 mm. of mercury systolic and 60 mm. diastolic. The leukocyte count was 18,300 (94 per cent neutrophils). The urine contained an occasional pus cell. The value for urinary diastase twenty-six hours after the onset of illness was 1,200 units.[19] The Wassermann reaction of the blood was negative. The patient received morphine for the relief of pain and fluids intravenously as needed. Recovery appeared to be complete, and she was discharged on March 12.

16. Amano, M., and Murata, M.: Tetanie bei akuten Abdominalerkrankungen, Zentralbl. f. Chir. **63**:694, 1936.

17. Foged, J.: The Diagnostic Value of Urine Diastase, Am. J. Surg. **27**: 439, 1935.

18. Elman, R.: The Variations of Blood Amylase During Acute Transient Disease of the Pancreas, Ann. Surg. **105**:379, 1937.

19. The unit of diastase is the same as that used by Foged, which he based on Wolgemuth's definition, "that solution, 1 cm. of which, under given conditions . . . is able to break down 1 cm. of 1 promille dissolved starch." [17]

Case 2.—O. B., a 36 year old obese white woman, entered the hospital on March 17, 1940 with the complaint that four days previously she had had a sudden severe pain in the abdomen at the level of the umbilicus. The pain had persisted but had gradually become dull in character. She had vomited from six to eight times a day. On admission her temperature was 99.8 F. and her pulse rate 80 per minute. Her blood pressure was 110 systolic and 75 diastolic. Examination revealed generalized tenderness and guarding of the abdomen, with the point of maximum tenderness in the midepigastrium. The leukocyte count was 11,900. A few pus cells were found in the urine. The urinary diastase reading on entry was 1,200 units, and two days later the value for blood amylase was 548 mg.[20] The patient continued to have abdominal pain and tenderness, accompanied by daily elevations of temperature to between 99.4 and 99.8 F. A cholecystogram disclosed many small rarefactions. On April 4 the gallbladder, containing many small calculi, was removed. No evidence of former pancreatitis was seen at operation. Recovery was uneventful, and the patient was discharged on April 17.

Table 2.—*The Values for Serum Calcium and Serum Lipids in Clinical Acute Pancreatic Necrosis* *

	Serum Calcium, Mg. per 100 Cc. Time Elapsed Since Onset of Illness (Days)															Lipids, Mg. per
Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	100 Cc.
1	.....	.....	7.0	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	584
2	.....	.....	.....	.....	.....	8.0	.....	.....	9.4	.....	.....	9.4	.....	.....	.....	167
3	9.6	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	197
4	.....	.....	8.3	.....	.....	.....	.....	9.7	.....	.....	.....	.....	.....	.....	.....	284
5	.....	.....	9.7	9.7	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
	.....	.....	.....	9.4	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
6	.....	.....	8.7	.....	.....	8.4	.....	.....	.....	.....	.....	.....	.....	.....	.....	544
7	9.5	.....	9.1	.....	9.4	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
	.....	.....	8.5	8.5	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
8	10.3	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
9	.....	.....	.....	.....	.....	.....	7.9	7.7	.....	7.4	7.6	.....	.....	13.4	11.2	381
	.....	.....	.....	.....	.....	.....	.....	7.7	.....	.....	8.1	.....	10.1	.....	.....	.....
10	.....	9.0	.....	8.9	8.8	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
11	.....	.....	.....	9.7	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
12	.....	.....	.....	.....	9.3	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....

* The serum lipids were determined at the time of the first measurement of serum calcium in 6 of 12 cases.

Case 3.—T. R., a 31 year old obese white woman, entered the hospital on March 23, 1940 because of severe, sharp, continuous pain in the epigastrium during the preceding twelve hours. The pain radiated through to the back. She had vomited about ten times. On examination the patient appeared to be in shock; the skin was cold and clammy; the temperature was 97 F., the pulse rate 72 per minute and the blood pressure 108 systolic and 80 diastolic. There was extreme tenderness but no rigidity in the epigastrium. The leukocyte count was 11,100. The urine contained albumin (3 plus). On entry the value for urinary diastase was 1,200 units and that for blood amylase 2,030 mg. The Wassermann reaction of the blood was negative. The treatment was conservative; 10 cc. of a 10 per cent solution of calcium gluconate was given intravenously every four hours for

20. The expression of the value for blood amylase in milligrams is based on Somogyi's sugar reduction method, cited by Elman.[18] The activity of the amylase is measured by the hydrolysis of a starch solution under given conditions, and the result is expressed in milligrams of sugar per hundred cubic centimeters of blood.

three days. Because of this therapy only one determination of serum calcium was made. The temperature varied from 101 to 102 F. for the first four days, then gradually returned to normal. The patient recovered and was discharged on April 4.

CASE 4.—V. C., a 45 year old Mexican, came to the hospital on March 30, 1940, after three days of severe epigastric pain and vomiting. He had been drinking heavily for a month. The temperature was 102.8 F., the pulse rate 130 per minute and the blood pressure 124 systolic and 80 diastolic. Both upper quadrants of the abdomen were rigid, and the left upper quadrant was extremely tender. The leukocyte count was 10,450. The icteric index was 38. The urinary diastase reading was 1,200 units. The patient received morphine and intravenous injections of a solution of dextrose. Improvement was rapid, and he was discharged on April 11.

CASE 5.—M. E., a 57 year old white woman, was admitted to the hospital on April 21, 1940. She gave a history of severe epigastric pain of four days' duration, with associated nausea and vomiting. The skin and scleras were slightly icteric (icteric index, 50). The abdomen was soft, but there was tenderness in the right upper quadrant, particularly over the gallbladder. The temperature was 98 F., the pulse rate 60 per minute and the blood pressure 165 systolic and 85 diastolic. The leukocyte count was 16,000. The value for urinary diastase was 600 units and that for blood amylase 2,835 mg. The patient received sedatives and intravenous injections of fluids; before the results of the serum calcium determinations were known, calcium gluconate was given intravenously. She improved and was discharged on May 18.

CASE 6.—J. E., a 50 year old white man, was admitted on April 27, 1940. He complained that he had awakened eight hours before admission with severe epigastric pain which radiated to the right upper quadrant of the abdomen and which was followed by vomiting and feverish sensations. He gave a history of chronic alcoholism and particularly heavy drinking for several days preceding the onset of illness. He was noticeably icteric (icteric index, 23). The gallbladder was enlarged and tender. The middle portion of the epigastrium was moderately tender but not rigid. The temperature was 103 F. and the pulse rate 120 per minute. The urine contained a trace of albumin and a few pus cells. The leukocyte count was 14,600. The value for urinary diastase was 600 units and that for blood amylase 1,425 mg. The Wassermann reaction of the blood was negative. Calcium gluconate was administered intravenously in addition to the usual conservative treatment. Icterus persisted, but otherwise the patient improved rapidly and was discharged on May 7.

CASE 7.—L. K., a 26 year old man, was admitted to the hospital on April 9 1940. Eight months before admission he had been in the hospital for distress of indefinite origin in the upper part of the abdomen. This had recurred several days before his second entry, and he had become jaundiced. The right upper quadrant of the abdomen and the epigastrium were tender and rigid. The icteric index was 80. He improved somewhat, but on May 6 he had a sudden onset of epigastric pain. Six hours after the onset the blood amylase reading was 218 mg. The value for urinary diastase was normal, and that for serum calcium was 9.5 mg. per hundred cubic centimeters. On the second day of illness the value for urinary diastase was 1,200 units. Calcium gluconate was administered intravenously, but the level of serum calcium fell slightly on the second and third day, as shown in table 2. The patient improved enough that on May 18 his diseased

gallbladder, containing multiple calculi, was removed. The pancreas was firm, enlarged and contained many pinhead-sized areas of healing fat necrosis. No stone was found in the common duct. Recovery was uneventful, and the patient was discharged on June 13.

Case 8.—W. D., a 52 year old Negro, was admitted to the hospital on May 21, 1940 because of epigastric and paraumbilical pain, which began suddenly seven hours before entry. The pain had increased in severity and had spread throughout the abdomen, which was boardlike in its rigidity. The point of maximum tenderness was in the midepigastrium. The temperature was 99 F., the pulse rate 84 per minute and the blood pressure 140 systolic and 96 diastolic. The leukocyte count was 15,600. The urine contained albumin (1 plus). On microscopic examination an occasional cast and a few pus cells were seen. The value for urinary diastase was 1,200 units and that for blood amylase 1,961 mg. The patient received morphine and a solution of dextrose intravenously. He felt much better the next morning and left the hospital without consent ten hours after entry.

Case 9.—J. B., a 63 year old Mexican, entered the hospital on May 23, 1940. He gave a history of severe epigastric pain, associated with nausea of three days' duration. The temperature was 101.6 F., the pulse rate 128 per minute and the blood pressure 128 systolic and 80 diastolic. Abdominal tenderness was extreme and generalized. The urine contained albumin (3 plus) and a few pus cells. The leukocyte count was 7,200. On the seventh day of illness the value for urinary diastase was 600 and that for blood amylase 125 mg. He received sedatives and fluids intravenously, including calcium gluconate beginning on the ninth day of hospitalization. Improvement was steady. The patient left the hospital free from any symptoms; he failed to return to the clinic for further checking, although he was urged to do so.

Case 10.—J. M., a 23 year old Mexican, was brought to the hospital on May 26, 1940, after an accident in which the automobile in which he was riding had collided with a train. The patient appeared to be in shock. His breath had an alcoholic odor. The rectal temperature was 98.2 F., the pulse rate 96 per minute and the blood pressure 60 systolic and 40 diastolic. There were many fresh abrasions of the skin. The leukocyte count was 19,800, with 96 per cent neutrophils. The value for urinary diastase on the second day of illness was 400 units. He received sedatives and fluids intravenously. Improvement was steady, and he was discharged on June 10.

Case 11.—A. D., a 39 year old white man, was admitted to the hospital on June 10, 1940 because of persistent nonradiating epigastric pain of five days' duration. He had been drinking heavily for some time before the onset of pain. On admission his temperature was 99 F., his pulse rate 100 per minute and his blood pressure 136 systolic and 96 diastolic. Both upper quadrants of the abdomen were tender but not rigid. The leukocyte count was 10,500. The value for urinary diastase was 400 units and that for blood amylase 434 mg. He received a solution of dextrose intravenously and sedatives. The patient apparently recovered and was discharged on June 20.

Case 12.—D. C., a 35 year old white woman, entered the hospital on Aug. 22, 1940, complaining of severe epigastric pain of thirty-six hours' duration, accompanied by repeated vomiting. The abdomen was distended, and there was extreme tenderness over the upper half. The temperature was 98 F., the pulse rate 100

per minute and the blood pressure 107 systolic and 80 diastolic. The leukocyte count was 9,600. The urine contained a faint trace of albumin. The value for urinary diastase was 2,400 units and that for blood amylase 1,618 mg. The calcium content of the blood was not determined until the fifth day of illness. The patient received the usual conservative treatment, improved rapidly and was discharged on September 2.

COMMENT

In only 1 of the 12 cases just summarized was the value for serum calcium above 10 mg. per hundred cubic centimeters, and in 7 cases it was below normal. The range was 7.0 to 8.8 mg. per hundred cubic centimeters. This was not unexpected in view of the amounts of calcium found in the lesions at necropsy in the first 3 cases reported in this paper. Values for serum calcium determined during the first day of illness (3 cases) were normal. In 1 case (L.K.) the value subsequently fell to 8.5 mg. per hundred cubic centimeters. In another (T. R.) the patient was in shock and intravenous calcium therapy was instituted, so that no further determination of calcium was made. In 6 of the 7 cases in which the value for serum calcium was low the subnormal level was reached on the third to the sixth day of illness. It is difficult to understand why the level of calcium remained low in 1 case (J. B.) for two days after calcium was given intravenously.

If it were possible to determine the serum calcium daily from the onset of the disease a greater number of low values might be obtained, but normal values would be expected unless the amount of fat necrosis was fairly extensive. It is known from the work of Rich and Duff [21] that both trypsinogen and lipase are concerned in the production of pancreatic necrosis. Our observations at necropsy taught us that either hemorrhagic lesions or fat necrosis may predominate. If the lesions are principally hemorrhagic there may not be enough fatty acids formed to require any appreciable amount of calcium in the formation of soaps.

Serum lipids were within normal range. We failed to observe any such increases in serum lipids as those reported by Binet and associates [8] and by Brunner.[9] It would appear that instances of severe hyperlipemia are rare. We also studied all cases of acute pancreatic necrosis for which there were necropsy records within recent years at the Los Angeles County Hospital. Specimens of lung tissue fixed in solution of formaldehyde U. S. P. were available in only 6 cases. Stains specific for fat revealed a few scattered droplets in the pulmonary vessels in 1 case. It seems inevitable that some absorption of fat and fatty acids must occur in extensive areas of necrosis. At least it is evident in 1 of our cases that abundant fat droplets were present in veins and lymphatics

21. Rich, A. R., and Duff, G. T.: Experimental and Pathological Studies on the Pathogenesis of Acute Hemorrhagic Pancreatitis, Bull. Johns Hopkins Hosp. **58**:212, 1936.

in the necrotic areas. It is questionable whether fatty acids by their own weak acidity contribute to the toxicity of the patient even if absorbed. The absorption of neutral fat, however, might be an important cause of death, in view of the autopsy observations in the case in which fat embolism occurred. Whether lack of available calcium and failure, therefore, to form soaps might favor absorption of the oleic fraction of the fatty acids at the point of origin of the acids is a matter for consideration.

CALCIUM THERAPY

The importance of calcium as a therapeutic agent cannot be evaluated, as it was used in only 3 of the last 12 cases reported, and, furthermore, it was employed only in conjunction with other therapeutic agents. In these 12 cases, in which there was a clinical picture of acute pancreatic necrosis, the record of therapeutic accomplishment is more favorable than one usually obtains. It must, of course, be recognized that the favorable outcome may be purely coincidental. We believe, however, that the use of calcium is indicated in cases of acute pancreatic necrosis, because it seems logical to assume that a plentiful supply of available calcium is desirable in order to facilitate the formation of calcium soaps in situ without undue depletion of the serum calcium.

SUMMARY

1. A case of acute pancreatic necrosis, tetany and fat embolism is reported.

2. A total in excess of 1,700 mg. of combined calcium was found in the pancreas, plus 2 Kg. of peripancreatic fat in another case of acute pancreatic necrosis (normal value, 78 mg. or less).

3. The level of serum calcium was below normal in 7 of 12 cases in which a diagnosis of acute pancreatic necrosis was made.

4. The value for serum lipids was normal in 6 of the aforementioned 12 cases.

5. Calcium therapy was employed in 3 of the 12 cases.

CONCLUSIONS

1. Fat embolism or severe hyperlipemia is rare in cases of acute pancreatic necrosis.

2. Considerable quantities of calcium may be present in the lesions in cases of acute pancreatic necrosis.

3. A moderate fall in the level of serum calcium of patients with acute pancreatic necrosis may occur between the third and the eleventh day of illness.

4. The effectiveness of calcium therapy should be evaluated after use in a larger number of patients.

CAPSULAR POLYSACCHARIDE IN THE BLOOD OF PATIENTS WITH PNEUMOCOCCIC PNEUMONIA

DETECTION, INCIDENCE, PROGNOSTIC SIGNIFICANCE AND RELATION TO THERAPIES

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We recently reported on the systematic examination for circulating capsular polysaccharide in the blood of 26 patients treated for pneumococcic pneumonia.[1] It is generally recognized that the presence of bacteremia increases the gravity of the prognosis of the disease. It appeared from our earlier observations that the occurrence of free polysaccharide, which is more rapidly detectable than bacteremia, makes the prognosis even graver.

In this paper are reported the cases of 109 additional patients with pneumonia due to Pneumococcus type I, II, III, IV, V, VII or VIII and are presented the data on 135 patients frequently studied for the presence of polysaccharide.

MATERIALS AND METHODS

The patients, who had ample clinical, and usually roentgenologic, evidence of lobar pneumonia, were studied in the pneumonia service of Harlem Hospital. Before treatment was instituted samples of sputum for typing and of blood for

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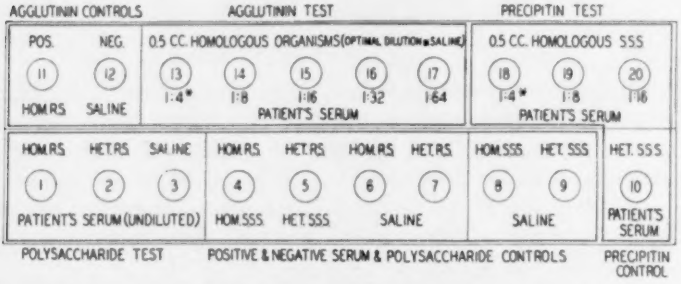
1. Bukantz, S. C.; Bullowa, J. G. M., and de Gara, P. F.: Detection of Capsular Polysaccharide in the Blood of Pneumococcic Pneumonias: Prognosis and Therapy, Proc. Soc. Exper. Biol. & Med. **41**:250, 1939; The Balance Between Capsular Polysaccharide and Antibody in Relation to Prognosis and Therapy of Pneumococcic Pneumonia, Ann. Int. Med. **14**:1348, 1941.

bacteriologic and immunologic examination were taken. After the types of pneumococci were known the patients were rotated for therapy with serum, with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) or with the two in combination. Whenever possible samples of blood were taken on the mornings of the second, third, fifth, eighth, eleventh and fourteenth days of hospitalization. When the disease persisted beyond the fourteenth day, samples of blood were examined at intervals determined by the course of the disease. The level of sulfapyridine in the blood was determined every forty-eight hours by the method of Bratton and Marshall [2] employing a photoelectric colorimeter. In some cases, urine, chest fluid or spinal fluid was studied.

Detection of Circulating Capsular Polysaccharide.—In the first 26 cases the method of Dochez and Avery [3] was used to determine the presence of circulating capsular polysaccharide.[1] In the subsequent 109 cases, because the "optimal" concentrations of antibody for detection of circulating capsular polysaccharide for each



0.5 CC. OF EACH REAGENT IN 10 X 75 mm. TUBES. CENTRIFUGATION - 2000 R.P.M - 30 MINUTES
RS - RABBIT SERUM (OPTIMAL DILUTION IN PHYSIOLOGIC SOLUTION OF SODIUM CHLORIDE)
SSS - CAPSULAR POLYSACCHARIDE (OPTIMAL DILUTION IN PHYSIOLOGIC SOLUTION OF SODIUM CHLORIDE)
HOM. - HOMOLOGOUS
HET. - HETEROLOGOUS
* FINAL DILUTION

Fig. 1.—Technic of detection of pneumococcic antigen-antibody balance in blood.

of the types of pneumococci under investigation had been determined,[4] it was unnecessary to make any dilutions of patient's serum. Five-tenths cubic centimeter of patient's serum is delivered into each of three 10 by 75 mm. pyrex tubes. Five-tenths cubic centimeter of the optimal dilution of homologous type-specific rabbit antibody solution is added to one tube, 0.5 cc. of a heterologous rabbit antibody solution to a second tube and 0.5 cc. of physiologic solution of sodium chloride to the third tube. Six additional positive and negative control tubes are prepared as indicated in figure 1. All tubes are centrifuged at 2,000

2. Bratton, A. C., and Marshall, E. K., Jr.: A New Coupling Component for Sulfanilamide Determination in Blood and Urine, J. Biol. Chem. **128**:537, 1939.

3. Dochez, A. R., and Avery, O. T.: Elaboration of Specific Soluble Substance by Pneumococcus During Growth, J. Exper. Med. **26**:477, 1917.

4. Bukantz, S. C., and de Gara, P. F.: The Detectability of Pneumococcal Polysaccharide and Antibody in Blood, Broth and Saline Solution (Optimal Concentration of Antigen and Antibody), J. Immunol. **39**:195, 1940.

revolutions per minute for thirty minutes.[5] When capsular polysaccharide is present in the serum, a precipitate appears in the first tube but not in the second and third. In all determinations the controls yielded the expected results. A precipitate may appear in the first tube because of antirabbit antibody present in the patient's serum during the course of serum sickness. In such instances, however, the second tube serves as a control, since it contains rabbit protein in contact with the patient's serum and therefore also yields a precipitate.

RESULTS

Incidence of Circulating Capsular Polysaccharide.—In Relation to Type of Pneumococcus and Severity of Disease: In table 1 are listed by type of pneumococcus the patients with detectable circulating capsular polysaccharide. The incidence of bacteremia and mortality is noted. All patients were accepted in the order of admission, without omissions because of mildness of disease. Circulating capsular polysaccharide was detected in the blood of 16 of the 135 patients (11.8 per cent). Only in the groups of patients with pneumonia due to Pneumococcus type I, III, VII or VIII were more than 15 patients studied. Circulating capsular polysaccharide was most frequently found among patients suffering from type III pneumococcus pneumonia, 11 of 40, or 27.5 per cent. Such patients were 68.7 per cent of all whose serum gave a

TABLE 1.—*Mortality Rate for All Patients and for Patients with a Positive Reaction for Circulating Capsular Polysaccharide*

Type of Pneumococcus	Total Series			Patients with Positive Reactions for Circulating Capsular Polysaccharide		
	Patients	Deaths	Percentage of Deaths	Patients	Deaths	Percentage of Deaths
I	32 5*	1 0*	3.1	0	0	
II	4 2*	0 0*	....	0	0	
III	40 7*	8 3*	20.0 43.0*	11 6*	7 3*	
IV	1 1*	1 1*	....	0	0	
V	9 3*	2 1*	....	0	0	
VII	33 10*	3 3*	9.1 30.0*	3 2*	2 2*	
VIII	16 3*	1 1*	....	2 2*	1 1*	
Total	135 31*	16 9*	11.8 29.1*	16 10*	10 6*	62.6 60.0*

* Bacteremia present.

5. de Gara, P. F.; Bukantz, S. C., and Bullowa, J. G. M.: Pneumococcal Capsular Polysaccharide in Urine: Detection by Precipitation and Centrifugation, J. Immunol. **37**:305, 1939.

positive reaction for capsular polysaccharide (11 of 16). This substance was also found in the serum of patients suffering from pneumonia due to Pneumococcus type VII or VIII—in 3, or 9.1 per cent, of 33 with type VII pneumococcus pneumonia and in 2, or 12.5 per cent, of 16 with type VIII pneumococcus pneumonia. The patients suffering from pneumonia due to Pneumococcus type I or VII were rated for the severity of disease on admission on the scale of Bullowa.[6] There were 32 patients with type I pneumococcus pneumonia, of whom 3 were rated as severely (50), 15 as moderately (50 to 70) and 14 as mildly (70 plus) ill on admission. Of 33 patients suffering from type VII pneumococcus pneumonia, 4 were severely, 10 moderately and 19 mildly ill. The patients with type I pneumococcus pneumonia were at least as severely stricken when first observed as were those with pneumonia due to the type VII pneumococcus.

In Relation to Bacteremia: In 31 of the 135 cases, or 23 per cent, bacteremia was present on admission. The incidence of bacteremia among the cases in which there was a positive reaction for capsular polysaccharide in the blood was 10 of 16, or 62.5 per cent, and among cases in which a negative reaction was obtained the incidence was 21 of 119, or 17.6 per cent. In 10, or 32.2 per cent, of 31 cases in which bacteremia was present the reaction for circulating capsular polysaccharide was positive, while it was positive in only 6, or 5.9 per cent, of 104 cases in which there was no associated bacteremia. It appears that while such a reaction was positive in approximately only one third of the cases in which bacteremia occurred, in almost two thirds of the cases in which the reaction was positive bacteremia was also present.

In Relation to Age: Of the 89 patients suffering from pneumonia due to Pneumococcus type III, VII or VIII, circulating capsular polysaccharide was found more frequently in those over 40 years of age (table 2 *A*). Only 1 of the 16 patients showing this substance in the blood was younger. Ten of the 16 were past 50 years of age (table 4).

In Relation to Sex and Duration of Disease: The first 16 cases of pneumonia caused by Pneumococcus type III, VII or VIII were confined almost entirely to the ward for male patients so that for determination of sex distribution only the last 73 cases have been analyzed. The distribution of cases in which there was a positive reaction for capsular polysaccharide in the blood was approximately the same for both sexes (table 2 *B*).

Although 56.3 per cent of the patients were first observed on the first to the fourth day of disease, only 6 (37.5 per cent) of the 16

6. Bullowa, J. G. M.: Use of Antipneumococcic Refined Serum in Lobar Pneumonia, J. A. M. A. **90**:1349 (April 28) 1928.

TABLE 2.—*Incidence of Detectable Circulating Capsular Polysaccharide in Relation to Age, Sex and Day of Disease on Which Patient Was Admitted to Hospital*

A. RELATION TO AGE IN EIGHTY-NINE PATIENTS WITH PNEUMONIA DUE TO PNEUMOCOCCUS TYPE III, VII OR VIII

Age of Patient	Total Series		Circulating Capsular Polysaccharide Present	
	Number of Patients	Percentage	Number of Patients	Percentage
Under 40 years	34	38.1	1	2.9
Over 40 years	55	61.9	15	27.3

B. RELATION TO SEX IN SEVENTY-THREE* PATIENTS WITH PNEUMONIA DUE TO PNEUMOCOCCUS TYPE III, VII OR VIII

Sex of Patient	Total Series		Circulating Capsular Polysaccharide Present	
	Number of Patients	Percentage	Number of Patients	Percentage
Male	51	69.8	8	15.7
Female	22	30.2	3	13.6

C. RELATION TO DAY OF DISEASE ON WHICH PATIENT WAS ADMITTED TO HOSPITAL IN EIGHTY-NINE PATIENTS WITH PNEUMONIA DUE TO PNEUMOCOCCUS TYPES III, VII OR VIII

Duration of Disease	Total Series		Circulating Capsular Polysaccharide Present	
	Number of Patients	Percentage	Number of Patients	Percentage
1 to 4 days	50	56.3	6	12.0
More than 5 days	39	43.7	10	25.4

* Sixteen patients with one of these types of pneumonia were observed in the original study, chiefly in the ward for male patients, and were excluded from sex incidence study.

TABLE 3.—*Relation of Detectability of Circulating Capsular Polysaccharide, Bacteremia and Mortality in Patients with Pneumococcic Pneumonia Treated with Sulfapyridine, Serum or a Combination of the Two*

	Total No. of Patients	Patients Recovered	Deaths	Mortality, Percentage	
1. No bacteremia; no circulating capsular polysaccharide	98	95	3	3.0	
2. Bacteremia; no circulating capsular polysaccharide	21	18	3	14.3	
3. No bacteremia; circulating capsular polysaccharide	6	2	4	66.7	
4. Bacteremia; circulating capsular polysaccharide	10	4	6	60.0	
	135	119	16	11.8	
All patients with associated bacteremia (2 + 4)	31	22	9	29.0	
All patients with a positive reaction for circulating capsular polysaccharide (3 + 4)	16	6	10	62.5	R.D.E.* 2.3

* R.D.E., ratio of difference to its error.

TABLE 4.—*Pertinent Data Concerning Patients with Pneumococcic Pneumonia*

Case No.	Age, Sex, Weight, Color	Type of Pneumococcus	Lobe Involved	Blood Culture, Day of Disease Blood Was Taken	Kind	Therapy: First Dose, Day of Disease	Therapy: Last Dose, Number of Hours Later	Therapy: Amount, Gm.	Level of Sulfapyridine in the Blood: Day of Disease	Level of Sulfapyridine in the Blood: Concentration of Free Drug per 100 Cc.
1	51 M 150 lb. W	III	R. L. L.	5th?, 7th, 8th, 9th, 10th —	Sp.	5th	209	66	6th 8th 10th 11th 12th 14th	2.3 5.5 2.1 5.5 5.0 2.8
2	60 F 180 lb. C	III	R. L. L.; L. L. L.	3d + 4th + (525 col.) 5th, 6th, 7th, 9th, 10th —	Sp.	4th 13th	160 88	54 25 } 79	5th 7th 8th 9th 14th	3.9 6.4 11.8 2.6 12.5
3	45 M 120 lb. W	III	L. U. L.	6th + 9th, contaminated 10th + 11th, 12th, 17th —	Sp.	6th	226	61	7th 8th 10th 11th 12th 13th 14th 17th	2.2 4.1 2.7 6.7 5.3 3.6 2.7 Trace
4	45 F 106 lb. C	III	R. U. L.	8th + (1,540 col.) 9th + 10th, 11th, 12th, 14th, 17th — 20th, 22d —	Sp.	8th 21st 35th	160 (15th day) 216 (29th day) 170 (42d day)	54 48 40 } 142	10th 11th 12th 14th 22d 26th 30th 39th 41st	8.0 10.2 4.4 7.6 7.8 9.8 2.6 9.0 12.6
5	56 F 150 lb. C	III	R. L. L.; spread to L. L. L.	2d + 6th, 7th, 9th —	Sp. and serum	2d 12th	252 (12th day) 6	102 495,000 U. S. P. units	2d 3d 4th 5th 6th 7th 8th 9th 10th 11th 12th 13th	2.5 4.7 3.6 2.2 2.0 0.0 4.1 5.7 3.4 20.0 14.3 4.9
6	35 M Wt.? C	III	R. L. L.; L. L. L.	1st, 2d, 3d —	Serum	1st	33	700,000 U. S. P. units	0	0
7	54 F Wt.? P. R.	III	R. U. L.; R. L. L.; empyema	Day of disease?; day of admission: 1st + (66 col.); 3d, 5th —	Sp.	Day in hospital 3d	66	16½	Day in hospital 4th 6th	4.3 1.8
8	47 M 135 lb. W	III	R. L. L.; R. U. L.	3d, 8th, 11th —	Sp. and serum	(a) 3d (b) 6th (c) 11th 3d	44 (5th day) 16 (7th day) 136 (17th day) 29	16 9 32 } 57 332,500 U. S. P. units	4th 9th 12th 14th 17th	8.8 1.8 4.6 8.5 6.6

* The following abbreviations have been employed: S.S.S., circulating capsular polysaccharide (specific soluble substance); upper lobe of the right lung; L.L.L., lower lobe of the left lung; L.U.L., upper lobe of the left lung; Sp., sulfapyridine; [illegible] ("Blood Culture" column) or a positive result for the precedure in question (in other columns); —, a negative result for [illegible]

Whose Blood Capsular Polysaccharide Was Detected *

	Serologic Studies						
Day of Disease	S. S. S.	AGT.	PPT.	S. S. S. in Urine, Day of Disease	Normal Temperature, Day of Disease	Outcome	Comment
5th to 11th	± B. or	—	—	13th +	41st	Recovery	Temperature continued elevated during administration of Sp.; convalescence marked by frequent brief elevations of temperature
daily studies	+ B.			17th +			
13th to 17th	± B. to ± P.	—	—	25th +			
19th to 44th	—	—	—				
3d	±	—	—		14th	Recovery	Temperature normal on 8th to 11th days; Sp. stopped on 11th day; S.S.S. still present; prompt recurrence of fever; disease controlled by resumption of Sp.
7th	+ B.	—	—				
9th	+ B.	—	—				
11th	± B.	—	—				
14th	± B.	—	—				
19th	+ B.	—	—				
th to 23d	+ B. or	—	—	11th +	38th	Recovery	Temperature first lowered beyond 100 on 11th day; occasional rises of temperature to between 100 and 101 until 38th day
	++ B.			31st —			
27th	± P.	—	—				
44th	±	—	—				
10th to 27th	+ B. to +++ B.	—	—	14th + 15th +	36th	Recovery	Three courses of Sp. required because of recurrence of disease on withdrawal of drug; small collection of fluid and air over R.U.L. throughout course of disease, which material was resorbed slowly and was never aspirated; transfusion 23th day
34th	+ B.			21st +			
38th	+ B.			47th +			
46th	+			104th —			
49th	+++ B.	—	—	126th —			
64th	++ P.	¼	—				
81st	+ P.	—	—				
104th	—	—					
126th	—	—	—				
3d	—	—	—		Never permanently normal	Death (14th day)	Large doses of Sp. given orally and intravenously; blood Sp. levels low but methemoglobin concentration 25%; three blood transfusions (250 cc.) given; Sp. withdrawn because of drop in white blood cells on 12th day; doses of serum followed by prompt elevation of temperature to 104 and progressive coma
4th	+ P.	—					
5th	+ P.	—	—				
7th	+ B.	—	—				
10th	± B.	—	—				
13th	—	1/10	⅛				
14th	—						
1st	—	—	—		Never	Death (4th day)	Considerable tachycardia and dyspnea on admission; digitalis (22 cat units) given in 15 hr.; pneumonia in lower lobes of both lungs; syphilitic aortitis and fatty degeneration of liver apparent at autopsy
2d	+	¼	—	2d +			
3d	—	1/10	¼				
in hospital 3d	+	1/32	—		Normal on 4th day of hospitalization; rose again on 5th day; elevated until death	Death (8th day of hospitalization)	Patient known to be diabetic for 10 yr.; pneumonia in R.L.L. two months before admission; diabetes difficult to control; small quantities of Sp. taken because of vomiting and withdrawn at time of thoracotomy 4 days ante mortem
4th	—	—	—		Drop to normal within 48 hr. after therapy started; return after cessation of Sp.	Death (17th day)	On 9th and 10th days chest fluid negative for Pneumococcus type III but S.S.S. found; on 12th day culture of chest fluid positive; thoracotomy and rib resection on day of death
6th	—	—	—				
7th	—	—	—				
10th	—	1/32	1/10				
13th	±	1/10	1/10				
17th	± P.	1/10	1/10				
	Chest Fluid						
9th	± B.	—	—				
10th	± B.	—	—				
12th	+ B.	—	—				
14th	++ B.	—	—				

., agglutinin; P.P.T., precipitin; R.L.L., lower lobe of the right lung; R.M.L., middle lobe of the right lung; R.U.L., on after centrifugation; P., precipitates after centrifugation; +, cultures positive for pneumococci obtained only in broth edure in question; col., colonies; H.S., horse serum; R.S., rabbit serum; I.V., intravenously, and I.T., intrathecally.

TABLE 4.—*Pertinent Data Concerning Patients with Pneumococcic*

Case No.	Age, Sex, Weight, Color	Type of Pneumococcus	Lobe Involved	Blood Culture, Day of Disease Blood Was Taken	Kind	Therapy: First Dose, Day of Disease	Therapy: Last Dose, Number of Hours Later	Therapy: Amount, Gm.	Level of Sulfapyridine in the Blood: Day of Disease	Level of Sulfapyridine in the Blood: Concentration of Free Drug, per 100 Cc.
9	58 M Wt.? C	III	L. L. L.; empyema	Day in hospital 2d — 24th —	Sp.	Day of disease?; day in hospital, 2d	256 (13th day)	67	Day in hospital 3d 5th 7th 10th 12th Chest Fluid 15th	2.0 4.5 3.9 7.4 6.0 10.0
10	54 M 163 lb. C	III	R. L. L.; L. L. L.	6th, not done 7th —	Sp.	7th	31	17	8th	6.5
11	69 M Wt.? C	III	L. U. L.; L. L. L. (no roentgenogram)	5th + (3,408 col.) 6th + (125 col.) 7th +	Sp.	5th	44	23	6th 7th	5.4 4.7
12	41 M 190 lb. C	VII	R. L. L.	3d —	Sp. and serum	(a) 4th (b) 11th 4th	67 (7th day) One dose	23 5 28 152,000 units	5th 7th	4.2 6.2
13	62 M Wt.? W	VII	L. L. L. (no roentgenogram)	8th, not done 9th + (3,225 col.) 10th + (41 col.) 11th, 12th, 13th, 14th —	Sp.	9th	132 (15th day)	49	10th 12th 13th 14th 15th	3.1 3.2 4.5 5.0 5.9
14	61 M Wt.? C	VII	R. U. L.; R. M. L.(?)	3d, 4th, 5th, 6th, 7th — 11th + (innumerable col.) 12th + (532 col.) 13th, 15th, 16th — 22d, 27th, 32d — 58th + (9 col.) 61st, 63d, 64th — 72d, 74th, 77th —	Serum and	(a) 3d (b) 12th (c) 60th (d) 74th	59 8 44 24	H. S. 304,000 units R. S. 990,000 units 1,294,000 units R. S. 500,000 units R. S. 540,000 units I. V. 65,000 units I. T. (62d day) R. S. 130,000 units I. T.	13th 15th 17th 19th 23d 56th 63d 65th 67th 69th	6.2 9.3 7.4 4.0 9.6 12.4 3.5 10.3 6.3 6.4
					Sp.	(a) 12th (b) 32d (c) 58th	204 (21st day) 124 (37th day) 432 (76th day)	64 34 138 236	72d 74th 76th 77th Spinal Fluid 61st 62d 64th 65th 66th 67th 69th 71st 72d 74th 75th Urine 77th	11.0 11.6 5.9 10.0 2.2 4.6 5.8 3.4 3.6 4.7 2.6 8.1 6.6 9.0 5.6 80.0
15	43 M 160 lb. C	VIII	R. L. L.; R. M. L.(?)	1st + (60 col.) 3d, 7th, 27th —	Sp. and serum	1st 1st	44 46	14 186,400 units	3d	9.2
16	51 F Wt.? C	VIII	R. U. L.	2d, not done 3d + (innumerable col.) 4th + 5th +	Sp.	3d	47	38	a.m. 4 p.m. 4 5	Trace 1.4 19.8

*neumonia in Whose Blood Capsular Polysaccharide Was Detected**—Continued

Day of Disease	Serologic Studies: S. S. S.	AGT.	PPT.	S. S. S. in Urine, Day of Disease	Normal Temperature, Day of Disease	Outcome	Comment
ay in hospital							
5th	+ B.			12th +	Normal from 4th to 15th day of hospitalization; rise to 102 F. on 16th day; operation on 18th day; normal for 3 days; irregular rises until death	Death (27th day of hospitalization)	Type III pneumococcus pneumonia in R.L.L. 6 weeks before final admission; prompt response to Sp. at that time; history for the 6 weeks before final admission not obtainable; patient severely dyspneic on admission from extensive empyema; S.S.S. and viable organisms always contained in chest fluid (see text)
6th	+ B.	—	—				
7th	++ B.	—					
9th	+ B.	—	—				
13th, 14th, 16th	+ B.	—	—				
19th	± P.	—	—				
20th	+ B.	—	—				
22d	± P.	—	—				
25th	± B.	—	—				
26th	±	—	—				
7th	++ B.	—	—		Never	Death (9th day)	
6th	++++ B.	—	—		Never	Death (7th day)	Number of circulating bacteria diminished under Sp. therapy, with slight fall of temperature but no clinical improvement
7th	++++ B.	—	—				
3d	± B.	—	—	8th —	5th day (12 hr. after onset of therapy)	Recovery	
9th	—	1/32	1/8	14th —			
14th	—	1/16	—				
17th	—	—	—				
9th	+ B.	—	—		Never	Death (15th day)	Extra large doses of Sp. given because of poor clinical response; condition progressively worse; death despite loss of detectable S.S.S. from blood and appearance and progressive increase of agglutinins
10th	± B.	—	—				
11th	—	—	—				
12th	—	1/4	—				
13th	—	1/8	—				
14th	—	1/16	—				
12th	+	—	—	55th +	3d -12th day–elevated	Death (78th day)	Fatal type VII pneumococcus meningitis; strain became sulfapyridine fast terminally
13th	++	1/8	1/8		13th-21st day–normal		
19th	+	1/32	1/4		22d -33d day–elevated		
22d	—	—	1/8		34th-41st day–normal		
26th	—	—	—		42d -44th day–slightly elevated		Cultures of Spinal Fluid
27th	±	—	—				59th day + (45,000 cells)
30th	+	1/8	—		45th-48th day–normal		
32d	++	1/4	—		49th-58th day–progressively elevating, culminating in chill		60th day +
33d	+	—	1/2				62d day +
35th	—	—	—				63d, 65th, 66th, 69th, 70th days, —
38th	—	1/4	—				71st day +
40th	+	1/8	—				74th day +
43d	+	1/8	—		58th-63d day–spiking		75th day + (2,800 cells)
45th	—	1/16	—		64th-65th day–normal		76th day —
50th	—	—	—		66th day –elevated		
54th	—	—	—		67th day –normal		
58th	—	—	—		68th-69th day–elevated		
61st	—	1/4	—		70th-71st day–normal		
62d	—	1/32	1/16		72d -death –progressive rise in temperature		
65th	—	1/64	1/8				
	Spinal Fluid						
69th		1/8	—				
71st	—	1/2	—				
72d	—	—	—				
After Serum							
2d	+ B.	1/16	1/16	4th —	Normal 3d to 6th day; slight rise; pleural effusion; slow return to normal	Recovery	
3d	± P.	1/64	1/16	11th +			
4th	—	1/64	1/16				
8th	—	1/8	1/4				
10th, 13th, 16th, 23d	—	—	—				
3d	+ P.	—	—	4th +	Normal first 24 hr. in hospital and again on 5th day for 24 hr.	Death (6th day)	
4th	++++ B.	—	—				
5th	+++ B.	—	—				

patients whose reaction for circulating capsular polysaccharide was positive were in this group. The remaining 10 (62.5 per cent) of the patients were in the group admitted after the fourth day of the disease (table 2 *C*).

Relation of Circulating Capsular Polysaccharide, Bacteremia and Mortality.—Among the 135 patients the mortality was 11.8 per cent. It was lowest (3 per cent) in the 98 patients with neither bacteremia nor capsular polysaccharide in the blood (table 3) and was approximately five times as great (14.3 per cent) among the 21 patients who had bacteremia but in whose blood capsular polysaccharide was not detected. The mortality among the 16 patients with circulating capsular polysaccharide was 62.5 per cent; only 6 of these 16 patients recovered. Among the 31 patients with bacteremia, with or without circulating capsular polysaccharide in the blood the mortality was 29 per cent. Among the 16 patients with capsular polysaccharide in the blood, with or without bacteremia, the mortality was 62.5 per cent.

Further separation of patients with a positive reaction for circulating capsular polysaccharide into those with and those without bacteremia yielded groups which were too small to permit statistically valid analysis. There was, however, no tendency for the mortality rates to be altered.

Description of Patients in Whose Blood Capsular Polysaccharide Was Found.—A detailed analysis of the cases of the 16 patients in whom blood capsular polysaccharide was found is given in table 4. Treatment was rotated after the type of pneumococcus had been determined in the sputum, irrespective of the presence of capsular polysaccharide in the blood. Ten of the patients with polysaccharide in the blood received sulfapyridine alone, 5 received serum and sulfpyridine and 1 received serum alone.

Patients Treated with Sulfapyridine Alone (cases 1, 2, 3. 4, 7, 9, 10, 11, 13 and 16; table 4): Of the 10 patients treated with sulfapyridine alone, 6 died (cases 7, 9, 10, 11, 13 and 16) and 4 recovered (cases 1, 2, 3 and 4).

Patients Treated with Sulfapyridine Alone Who Died: Three patients (cases 10, 11 and 16) with uncomplicated pneumonias received sulfapyridine continuously to the time of death; after a total of 17 to 38 Gm. of sulfapyridine was taken all had blood levels of the drug generally considered satisfactory (2 to 8 mg. per hundred cubic centimeters). These patients died after two and in less than four days of hospitalization, on the ninth, seventh and sixth day of the disease, respectively. Two of the patients (cases 10 and 11) showed no evidence of clinical improvement, although the number of organisms in the blood

culture of the patient with bacteremia was reduced (case 11).[7] The third patient (case 16) improved temporarily, as indicated by return of the temperature to normal, but the fever recurred and he died on the sixth day of disease. Antibodies were not detected in the blood of these patients.

In case 13 (fig. 2) the patient was admitted on the eighth day of his disease. On the ninth day, when therapy was initiated, bacteremia was present. A total of 49 Gm. of sulfapyridine was given during the next five and one-half days, and a sulfapyridine level of 5.9 mg. per hundred cubic centimeters of blood was obtained. The blood was sterilized in two days, and capsular polysaccharide, which had been

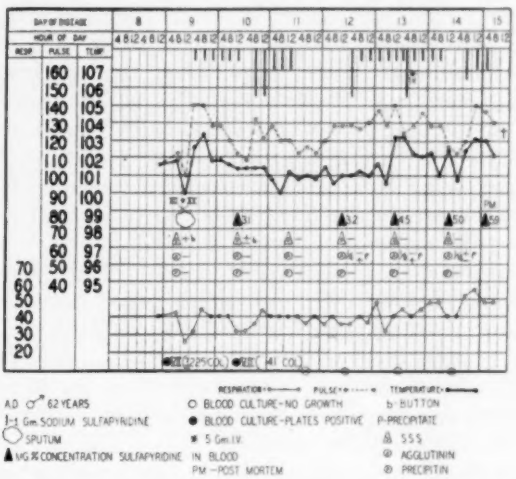


Fig. 2 (case 13).—Course of illness and presence of circulating capsular polysaccharide (S. S. S.).

present in the first sample of blood tested, disappeared two days later. This disappearance was followed by a gradually increasing agglutinin titer, though the temperature remained elevated and the patient died.

The remaining 2 patients (cases 7 and 9) presented empyema due to Pneumococcus type III on admission; for neither was the history

7. The simultaneous occurrence of circulating capsular polysaccharide and homologous precipitin in this case has been described previously and an explanation attempted, based on the possible lack of uniformity between the circulating capsular polysaccharide of the patient, the antibody injected and the antibody used to test for the polysaccharide.[1] In cases 8 and 15 the same phenomenon was demonstrable, although for a shorter period.

of the onset of the disease obtainable. The first of these (case 7), who had bacteremia on admission, had been known to be diabetic for ten years, and the diabetes was controlled with difficulty during her stay in the hospital. She received 16.5 Gm. of sulfapyridine during the first sixty-six hours in the hospital and had a level of 4.3 mg. of the drug per hundred cubic centimeters of blood. Administration of sulfapyridine was stopped after rib resection, and the patient became progressively worse and died. The second patient (case 9) had been discharged from the hospital (eleven weeks before the final admission) after recovery from type III pneumococcus pneumonia treated with sulfapyridine. Because of the severity of his illness and the intensity of dyspnea on readmission, a history of the interval could not be obtained. A total of 67 Gm. of sulfapyridine was given during the next eleven and one-half days, which resulted in a level of 7.4 mg. of the drug per hundred cubic centimeters of blood and a level of 10 mg. per hundred cubic centimeters of chest fluid. Despite continuation of therapy, the chest fluid continued to yield type III pneumococci on culture and contained considerable amounts of circulating capsular polysaccharide on all examinations. Large quantities of pus were removed on two occasions, and the temperature reached normal. Three days after cessation of therapy with sulfapyridine the temperature became elevated, and two days later a rib resection was done, after which the patient, despite irregular rises of temperature, improved. Throughout this period, and up to the day before death, capsular polysaccharide was detectable in the blood, and cultures of material from the wound continued to yield pneumococci of type III. Antibodies were never detected in the blood. On the twenty-seventh day the patient died suddenly; permission for a post-mortem examination was not obtained.

Patients Treated with Sulfapyridine Alone Who Recovered: The course of the disease in the 4 patients who recovered under treatment with sulfapyridine alone (cases 1, 2, 3 and 4) was characterized by a prolonged fever which subsided slowly during administration of the drug (fig. 3) or recurred promptly when the drug was discontinued (fig. 4). The capsular polysaccharide remained in the blood for many days; either a slight amount of antibody appeared later or there was none at all. In cases 2 and 4 several courses of therapy with sulfapyridine were given, and in case 4 [7] capsular polysaccharide was detectable in the blood for at least eighty-one days.

Patients Treated with Serum and Sulfapyridine: Of the 5 patients (cases 5, 8, 12, 14 and 15) treated with serum and sulfapyridine, 3 (cases 5, 8 and 14) died and 2 (cases 12 and 15) recovered.

Patients Treated with Serum and Sulfapyridine Who Died: In 2 of the 3 cases with a fatal outcome, treatment with serum and with

sulfapyridine was not initiated simultaneously. In case 5 (fig. 5) the patient was in the group treated with sulfapyridine and received the drug alone until the twelfth day of disease. The temperature had been almost normal for thirty-six hours; although there seemed to be some

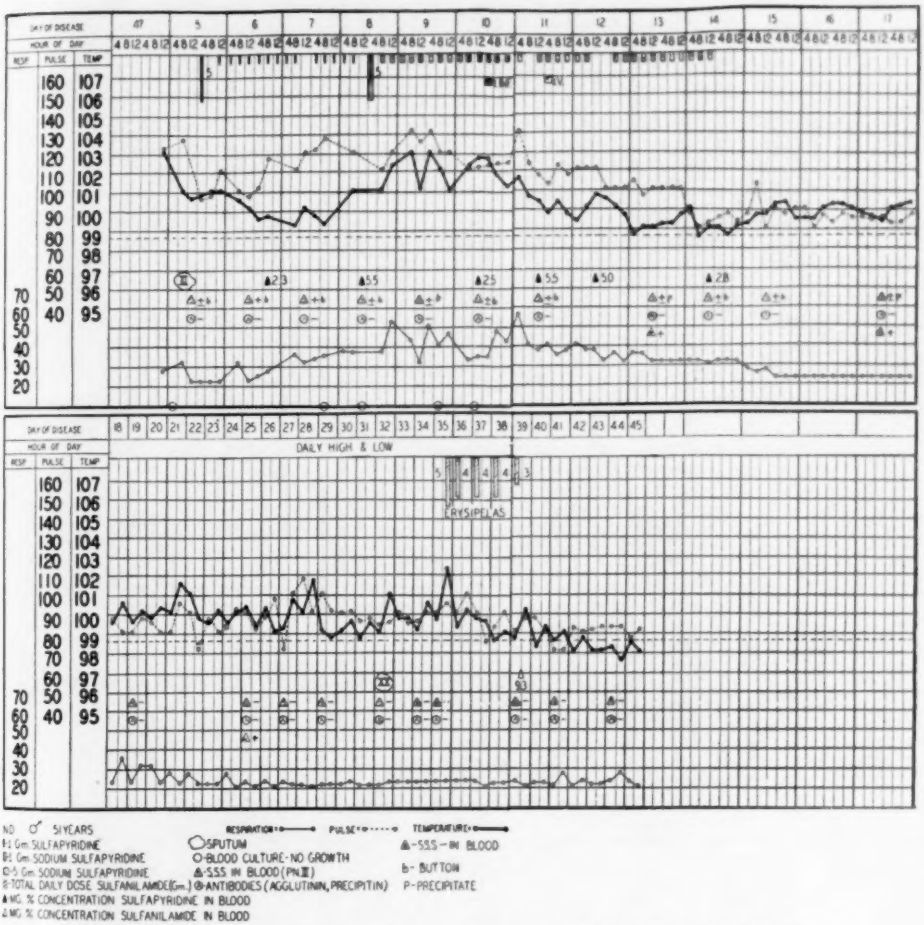


Fig. 3 (case 1).—Course of illness and presence of circulating capsular polysaccharide (S. S. S.).

clinical improvement, capsular polysaccharide was still detected in the blood, though in diminishing concentration. Because the leukocyte count dropped to 2,600 therapy with sulfapyridine was discontinued, and

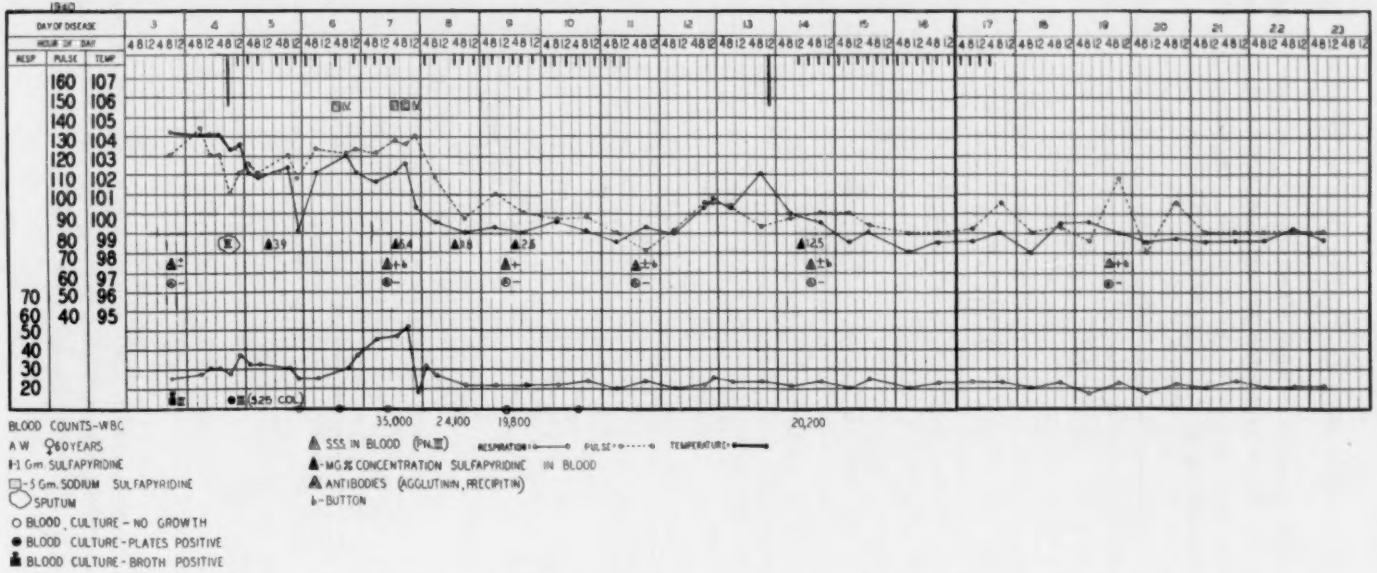


Fig. 4 (case 2).—Course of illness and presence of circulating capsular polysaccharide (S. S. S.).

because capsular polysaccharide was present in the blood specific serum was administered. In all, 495,000 U. S. P. units of refined and concentrated rabbit antipneumococcus serum was administered. The capsular polysaccharide disappeared and a moderately high titer of antibodies appeared in the blood. The temperature rose again; the patient became stuporous and died forty-eight hours later.

In case 14 the patient was originally in the group treated with serum. After 1,294,000 U. S. P. units of therapeutic horse and rabbit antipneumococcus serum alone had failed to control the disease and the patient appeared to be moribund, he was given serum and sulfapyridine simultaneously. Capsular polysaccharide was present in the

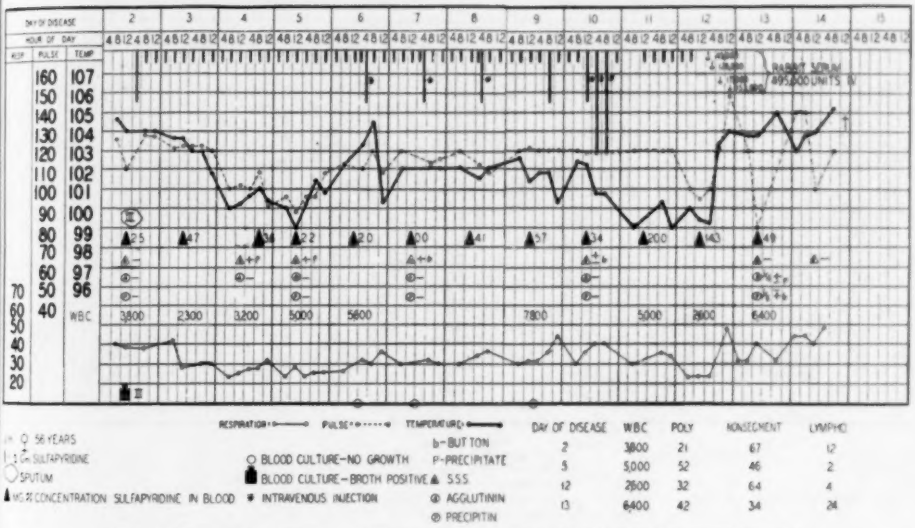


Fig. 5 (case 5).—Course of illness and presence of circulating capsular polysaccharide (S. S. S.).

blood at this time and persisted for at least eight days (precipitin was also present in the blood), then disappeared as the patient's clinical condition improved.[7] On several occasions after cessation of treatment, capsular polysaccharide reappeared in the blood and was associated with recrudescence of the fever. On each occasion the capsular polysaccharide disappeared from the blood, and the fever subsided when administration of the drug was resumed. Finally, meningitis developed, which did not respond to administration of both drug and serum; the strain of pneumococci had become sulfapyridine fast. The patient died on the seventy-eighth day of disease.

In the third case (8, fig. 6) the patient received sulfapyridine and serum simultaneously on the third and fourth days of his disease; on the fourth day his blood did not contain capsular polysaccharide. Although 332,500 U. S. P. units of therapeutic rabbit antipneumococcus serum (type III) was given within twenty-nine hours and a total of 16 Gm. of sulfapyridine during the first forty-four hours, antibodies were not detected in the blood. The temperature returned to normal at this time, and the administration of sulfapyridine was discontinued, after which the temperature became elevated. On the sixth day of disease 6 Gm. of sulfapyridine was given and on the seventh day 3 Gm. in sixteen hours; then its administration was again stopped. The

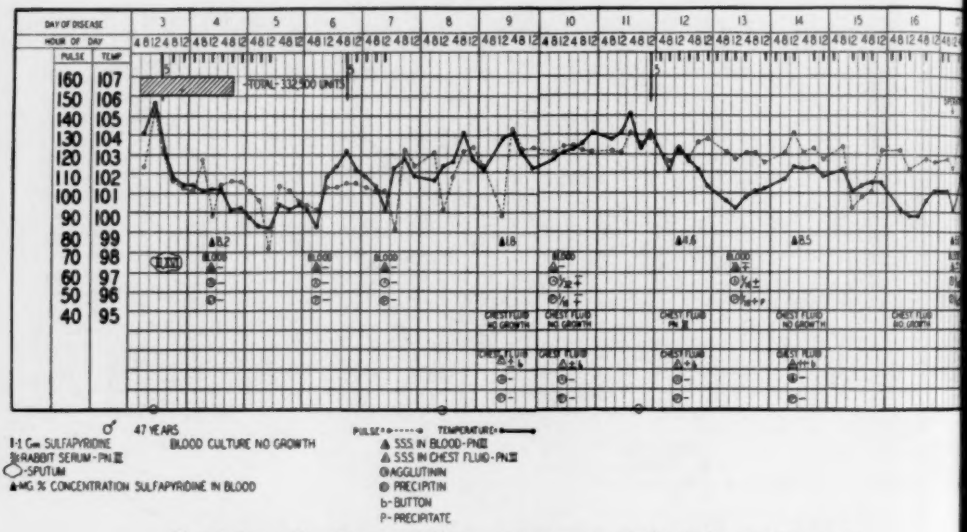


Fig. 6 (case 8).—Course of illness and presence of circulating capsular polysaccharide (S. S. S.).

temperature remained elevated, and signs of fluid appeared at the base of the right lung. On the ninth and tenth days pleural fluid obtained by aspiration was sterile on culture, although it contained capsular polysaccharide. For the first time, on the tenth day, antibodies appeared in the blood. On the eleventh day, because of increasing severity of illness administration of sulfapyridine was again started, a total of 32 Gm. being given during one hundred and thirty-six hours. Pleural fluid aspirated on the twelfth day contained living pneumococci and capsular polysaccharide; that on the fourteenth and sixteenth days, however, was sterile but contained the polysaccharide on the fourteenth day. Circulating capsular polysaccharide was first detected on the

thirteenth day of disease and was present simultaneously with precipitin and agglutinin for at least five days.[7] The patient remained severely ill; thoracotomy and rib resection were performed on the seventeenth day of disease, and he died that day.

Patients Treated with Serum and Sulfapyridine Who Recovered: The 2 patients (cases 12 and 15) who recovered under treatment with serum and sulfapyridine made the most satisfactory responses of the entire series. In both patients circulating capsular polysaccharide was present on admission, and both received a relatively small total quantity of serum and sulfapyridine simultaneously. There was prompt disappearance of the polysaccharide from the blood and equally prompt appearance of antibody, these being simultaneously present in case 15.[7]

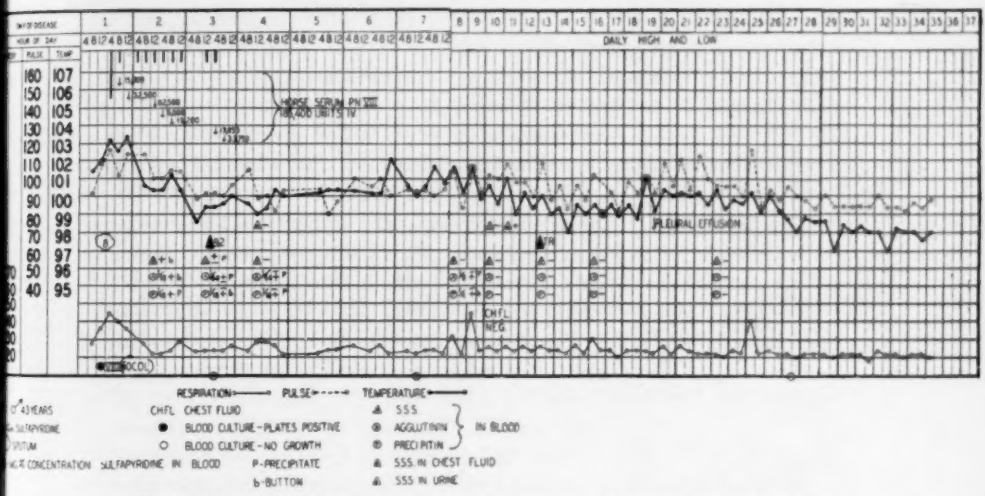


Fig. 7 (case 15).—Course of illness and presence of circulating capsular polysaccharide (S. S. S.).

The temperature fell in case 12 within twelve hours after initiation of therapy and remained normal thereafter. The convalescence in case 15 (fig. 7) was complicated by the development of a sterile pleural effusion. The temperature was slightly elevated during the pleural effusion and became normal when the fluid was absorbed.

Patient Treated with Serum Alone: The sixteenth patient (case 6) whose serum gave a positive reaction for capsular polysaccharide received only serum. This patient died despite rapid neutralization of circulating capsular polysaccharide and the presence of antibodies in the blood. Capsular polysaccharide was first detected after intravenous administration of therapeutic antipneumococcus serum.

COMMENT

The incidence in the entire series of cases in which there was a positive reaction for circulating capsular polysaccharide was 11.8 per cent (table 1); however, among the cases of pneumonia due to Pneumococcus type III, VII or VIII alone the incidence was 17.9 per cent. Capsular polysaccharide in the blood in cases of pneumonia due to one of these types is not infrequent.

It is apparent that the type of the infecting pneumococcus, the age of the patient and the duration of disease before treatment is initiated are factors which influence the appearance of capsular polysaccharide. In the present series the polysaccharide was not detected in the blood of patients with type I pneumococcus pneumonia [8] and occurred in more than one quarter of the patients with type III pneumococcus pneumonia. In patients with pneumonia due to the type VII or VIII pneumococcus (table 1), it appeared less frequently, in approximately 10 per cent. It also occurred in patients with pneumonia due to Pneumococcus type XI, XX or XXXIII and among patients studied less systematically later with pneumonia caused by Bacillus Friedländer A. Pneumococci of type III form large capsules and produce large quantities of capsular polysaccharide as compared with pneumococci of type I. The poorer response of infections caused by the type III pneumococcus to serum therapy, as compared with the responses of infections due to the type I or type VII pneumococcus and some other organisms may be due to this characteristic. It is also possible that the carbohydrate of Pneumococcus type III is less firmly bound to the organism than are the carbohydrates of other types of pneumococci. Since the studies of Cole [9] on infected exudates and serums of patients with pneumococcic pneumonia it has been known that circulating capsular polysaccharide neutralizes antibody in vitro, and Downie [10] demonstrated the neutralization of antibody by capsular polysaccharide in vivo. The occurrence of neutralization of antibody by capsular polysaccharide is suggested in case 8 of the present series. This patient received 332,500 U. S. P. units of antipneumococcus rabbit serum type III on the third and fourth days of disease. Antibodies were first detected on the tenth day of disease, a fact which suggested either that the antibody was autogenous,

8. Park and Cooper detected traces of a "specific toxic substance" (believed to be soluble specific substance neutralized by antibody) in the late toxic stage of 4 cases of type I pneumococcus infections (Bullowa, J. G. M.: Lobar Pneumonia and Its Treatment with Refined Sera, in Alexander, J.: Colloid Chemistry, New York, The Chemical Catalog Company, 1928, vol. 2, p. 793).

9. Cole, R. I.: Neutralization of Antipneumococcus Immune Bodies by Infected Exudates and Sera, J. Exper. Med. **26**:453, 1917.

10. Downie, A. W.: Experiments with Type-Specific Pneumococcus Polysaccharides in Rabbits, J. Path. & Bact. **45**:149, 1937.

and not the one introduced, or that it had been liberated from capsular polysaccharide at the time it was detected. Capsular polysaccharide was not detectable in the blood during this period, though the pleural fluid contained large amounts of the substance on the ninth and tenth days of disease. Both these fluids were sterile on culture. In Finland's [11] experience, capsular polysaccharide was not detectable in fluid from sterile pleural effusions. Diffusible substances in the blood appear in greater concentration in an area of inflammation. It is probable, therefore, that capsular polysaccharide was present in the blood in case 8 in subdetectable quantities and was concentrated in the inflamed pleural cavity. The subdetectable amount of circulating capsular polysaccharide may have been sufficient to neutralize the injected antibody. Larger and detectable quantities of circulating capsular polysaccharide will neutralize larger amounts of antibody.

The second factor, the age of the patient, appears to be of considerable importance in conditioning the appearance of capsular polysaccharide in the blood. This relation is demonstrated by the data in table *2 A*, which indicate a significantly greater incidence in the older age group of cases in which there was a positive reaction for circulating capsular polysaccharide.

The third factor, duration of disease, seems to be of less importance than the age of the patient, although there is some indication that the incidence of capsular polysaccharide in the blood is greater in those admitted to the hospital after the fourth day of their disease (table *2 C*). An analysis of the cases of type III pneumococcus pneumonia alone, however, shows no significant difference in the incidence of capsular polysaccharide in the early and in the late stages of infection (among 20 cases of the early stage—first to fourth day—there were 5 in which the reaction for capsular polysaccharide was positive; among 20 cases of the late stage—fifth day or later—there were 6 in which the reaction was positive).

The increased fatality rate associated with the presence of capsular polysaccharide in the blood of patients with pneumococcic pneumonia is clearly indicated in table 3. The mortality for the whole series was 11.8 per cent, a figure similar to the mortality rate of a large reported series of cases of treated pneumococcic pneumonias.[12] In the presence of bacteremia the mortality rose to 29 per cent, while in the presence of circulating capsular polysaccharide 62.5 per cent of the patients died.

11. Finland, M.: Immunological Reactions of Pneumonic Pleural Fluids, J. Exper. Med. **55**:169, 1932.

12. Lord, F. T.; Robinson, E. S., and Heffron, R.: Chemotherapy and Serum Therapy of Pneumonia, New York, Commonwealth Fund, Division of Publications, 1940, chap. 8, p. 62.

Cohn and Lewis [13] found that the fatality rate increased in relation to the number of lobes involved. In their cases involvement of four lobes was associated with a mortality of 68.2 per cent, while there was a 40.7 per cent mortality when only three lobes were involved. The increased fatality rate in cases in which there was a positive reaction for circulating capsular polysaccharide is not correlated with the number of lobes involved, because in 7 patients only one lobe was affected; two lobes were affected in the remaining 9, and there was none with more than two pneumonic lobes. Corresponding figures reported by Cohn and Lewis were 8.5 per cent for cases in which one lobe was involved and 24.5 per cent for cases in which two lobes were involved.

Spring, Lowell and Finland [14] demonstrated that the growth inhibition and pneumococcidal action of sulfapyridine in vitro is not affected by the addition of capsular polysaccharide. Accordingly, mechanism by which capsular polysaccharide increases fatality must be sought in the effect of that substance on the immune mechanisms important for recovery. Early observations by Rosenow [15] and by Tchistovitch and Yourevitch,[16] confirmed and extended by a number of other workers,[17] demonstrated that capsular polysaccharide was specifically antiopsonic and therefore specifically inhibited phagocytosis. Rosenow [15] and Felton and Bailey [18] have demonstrated that capsular polysaccharide specifically makes avirulent pneumococci virulent and augments the virulence of virulent organisms. The effectiveness of sulfapyridine in control of pneumococcic infections is the result of the combined bacteriostatic activity of the drug and of the immune substances which develop during

13. Cohn, A. F., and Lewis, W. H.: Lobar Pneumonia and Digitalis, Am. J. M. Sc. **189**:457, 1935.

14. Spring, W. C.; Lowell, F. C., and Finland, M.: Studies on the Action of Sulfapyridine on Pneumococci, J. Clin. Investigation **19**:163, 1940.

15. Rosenow, E. C.: Human Pneumococcal Opsonin and the Antiopsonic Substance in Virulent Pneumococci, J. Infect. Dis. **4**:285, 1907.

16. Tchistovitch, N., and Yourevitch, V.: Sur les opsonines et les antiphagines dans l'infection pneumococcique, Ann. Inst. Pasteur **22**:611, 1908.

17. Wadsworth, A. B., and Sickles, G. M.: The Effect of Type I Pneumococcus Culture Broth on the Phagocytic Action of Type I Pneumococcus Serum, J. Immunol. **14**:321, 1927. Sickles, G. M.: Further Observations on the Effect of Type I Pneumococcus Culture Broth on the Phagocytic Action of Type I Pneumococcus Serum, ibid. **14**:329, 1927. Sia, R. H. P.: Studies on Pneumococcus Growth Inhibition: VI. The Specific Effect of Pneumococcus Soluble Substance on the Growth of Pneumococci in Normal Serum—Leucocyte Mixtures, J. Exper. Med. **43**:633, 1926. Ward, H. K.: Observations on the Phagocytosis of the Pneumococcus by Human Whole Blood: I. The Normal Phagocytic Titre, and the Antiphagocytic Effect of the Specific Soluble Substance, ibid. **51**:675, 1930.

18. Felton, L. D., and Bailey, G. H.: Biologic Significance of the Soluble Specific Substances of Pneumococci, J. Infect. Dis. **38**:131, 1926.

the course of the disease. Reichel's [19] observations indicate that immune bodies may exert their effects early in the course of an experimental pneumococcic infection, since the serums of rabbits already exhibit specific bacteria-clearing properties one hour after the intravenous inoculation of living pneumococci. An increase of capsular polysaccharide in the blood of patients with pneumococcic pneumonia may be accompanied by "neutralization" of antibodies. Furthermore, Tunnicliff [20] showed that sulfapyridine promotes phagocytosis in plain broth but not in dextrose broth cultures of pneumococci. She suggested that this may be related to an increased concentration of capsular polysaccharide in the dextrose broth cultures as compared with the concentration in plain broth cultures.

It is suggested that specific antibody be administered to those patients in whom circulating capsular polysaccharide is detected so that the anti-immune effects of the latter may be neutralized.

SUMMARY

Systematic determination of capsular polysaccharide, agglutinin and precipitin titers were made on samples of blood of 135 patients with pneumonia caused by pneumococci of types I (32 cases), II (4 cases), III (40 cases), IV (1 case), V (9 cases), VII (33 cases) and VIII (16 cases) in a series rotated for treatment with sulfapyridine, with serum or with the two in combination.

Capsular polysaccharide was detected in the blood of 16 patients, or 11.8 per cent of the entire series. Eleven of the 16 had type III, 3 had type VII and 1 had type VIII pneumococcus pneumonia.

There was a significantly greater incidence of positive reactions for circulating capsular polysaccharide in the older age group, a tendency to greater incidence with increasing duration of disease and an equal sex incidence.

The mortality for the patients in whose blood capsular polysaccharide was present was 62.5 per cent, while the mortality for all the patients with bacteremia was only 29 per cent and the mortality for the entire series was 11.8 per cent. The mortality for the patients without bacteremia and without capsular polysaccharide in the blood was only 3 per cent.

Of the 10 patients whose serum gave a positive reaction for capsular polysaccharide and who were treated with sulfapyridine alone, 6 died. The illness of the 4 patients recovering under sulfapyridine therapy

19. Reichel, H. A.: Studies on Pneumococcal Immunity, Proc. Staff Meet., Mayo Clin. **14**:636, 1939.

20. Tunnicliff, R.: Effect of Sulfapyridine on Phagocytosis and Dissociation, J. Infect. Dis. **66**:148, 1940.

alone ran a prolonged course, with a tendency to recurrence of fever, slow disappearance of capsular polysaccharide from the blood and failure to produce antibody.

Of the 5 patients whose serum gave a positive reaction for capsular polysaccharide and who were treated with both sulfapyridine and serum, 3 died; 2 of these did not receive serum and sulfapyridine simultaneously, while the third received insufficient sulfapyridine. The 2 patients recovering after simultaneous serum and sulfapyridine therapy made much more satisfactory clinical responses. The sixteenth patient in whose blood capsular polysaccharide was detected died after treatment with serum alone.

The influence of capsular polysaccharide on the clinical course of illness in these patients is discussed.

Miss Ruth Mayer assisted in the titrations of capsular polysaccharide and of antibodies on most of the patients.

Miss Constance Lebair and Miss Evelyn Greenbaum assisted in the preparation of the manuscript.

RETINAL ARTERIOVENOUS NICKING

RELATION TO ENLARGEMENT OF THE HEART IN AMBULATORY PATIENTS WITH HYPERTENSION

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SAN ANGELO, TEXAS

When you cannot measure, your knowledge is meager and not satisfactory. —Lord Kelvin.

There are a number of changes visible in the retinal arteries and veins of patients with early or late hypertension. The most frequent are narrowing of the arteries (spasm), changes in caliber (so-called spasm or atheroma), tortuosity, mottling of the arterial reflex, "silver wire" arteries and arteriovenous nicking. We have chosen the last of these lesions for study because (1) arteriovenous nicking is easily and accurately identified after one has sufficient practice, (2) it is the most constant change present in all forms of long-standing hypertension and (3) it never occurs except in patients who have or have had hypertension. Wagener has stated that "spasm" never occurs except in hypertensive patients. Our experience has confirmed this repeatedly, but the phenomenon is largely confined to patients with exceedingly high diastolic pressure (so-called malignant hypertension) and consequently is not commonly seen. This lesion (spasm) has no relation to the size of the heart or the duration of the disease but is important in diagnosis.

Arteriovenous nicking (fig. 1) was first described by the English ophthalmologist Gunn [1] late in the nineteenth century (1883). O'Hare and Walker,[2] in 1922, pointed out that this lesion, along with changes in caliber in the retinal arteries, was present in their arteriosclerotic patients who had hypertension but not in the nonhypertensive patients.

From the cardiac clinics of Baylor University and Parkland Hospital.

1. Gunn, R. M.: Peculiar Appearance of the Retina in the Vicinity of the Optic Disk Occurring in Several Members of the Same Family, Tr. Ophth. Soc. U. Kingdom **3**:110, 1883.

2. O'Hare, J. P., and Walker, W. G.: Arteriosclerosis and Hypertension, Arch. Int. Med. **33**:343 (March) 1924.

It was at first believed that the lesion was produced by the pressure of the hypertensive artery on the vein, but this was none too logical, since the lesion persisted after the pressure had fallen to normal. Moreover, Friedenwald,[3] in 1929, showed that the lesion was really a fibrotic change at the crossing of the artery and the vein. It is for this reason that we use the term arteriovenous nicking instead of arteriovenous compression. A better term would be arteriovenous fibrosis. It is now generally agreed that this phenomenon occurs only in hypertensive patients (Thiel,[4] Volhard,[5] Wagener,[6] and others). In our combined experience with

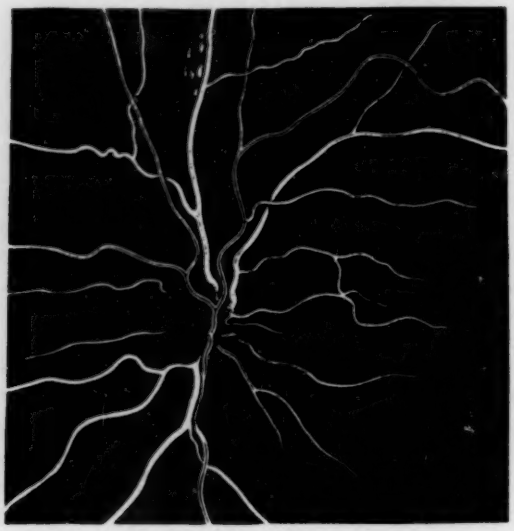

Fig. 1.—The first drawing of the lesions of the retinal arteries and veins designated as arteriovenous nicking (reproduced from Gunn [1]).

hospital, clinic and private patients during the past ten years, we have found no exceptions to this rule. One must be most careful to distinguish

3. Friedenwald, J. S.: The Pathology of the Eye, New York, The Macmillan Company, 1929.

4. Thiel, R.: Significance of Examination of the Eyes for the Diagnosis and Differential Diagnosis of Hypertension and Kidney Diseases, Klin. Wchnschr. **15**:1785 (Dec. 5) 1936.

5. Volhard, F.: The Significance of the Examination of the Eyes for the Understanding of Hypertension and Kidney Diseases, Klin. Wchnschr. **15**:1745 (Nov. 28) 1936.

6. Wagener, H. P.: The Clinical Interpretation of Retinal Vascular Lesions in Hypertension, Pennsylvania M. J. **40**:705 (June) 1937.

between slight compression of the vein by the artery and definite arteriovenous nicking (fig. 2). Slight compression may be found in persons who have never had hypertension. This distinction is discussed more fully in subsequent paragraphs of this paper.

For some years it has been obvious to us, and doubtless to many others, that there must be a close relation between this phenomenon and enlargement of the heart in hypertensive states, since both signs appear late in the course of the disease. This research was undertaken

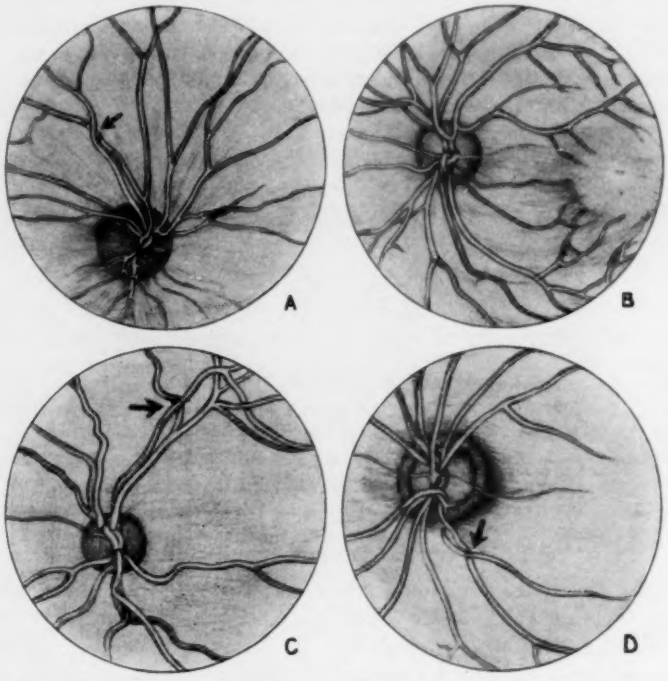

Fig. 2.—The degrees of arteriovenous nicking. *A*, definite; *B*, none (normal retinal arteries and veins); *C*, early, and *D*, moderate.

to determine as precisely as possible the exactness of this relation. In order to secure the greatest accuracy in the retinal examinations one person (S. A. S.) did all the examining, through dilated pupils only. The greatest difficulty, however, was encountered in the determination of the presence of enlargement of the heart. We feel that by applying the same rules of measurement and the same roentgenologic technic in each case and comparing the various subgroups with each other, we have,

with fair satisfaction, overcome this obstacle. It remains, however, the bête noire in all studies of this sort and for that reason is discussed more adequately in subsequent paragraphs.

METHOD

All the patients (317) included in this study were ambulatory and were in the private practice of one of us (S. A. S.) or were attending the cardiac clinics (table 1). Each patient's history was carefully obtained and the physical examination carefully made, the data being recorded on a form similar to that recommended by the American Heart Association. A careful retinal study was made by one of us (S. A. S.) before the heart was examined. A teleroentgenogram and an electrocardiogram were made for each patient, as well as a urinalysis and a Kline test. Other examinations were made when indicated.

TABLE 1.—*The Distribution According to Age, Sex, Average Blood Pressure and Race of Three Hundred and Seventeen Patients with Hypertension*

Average age, years	53.7	
Lowest	27	
Highest	82	
	Number	Percentage
Females	176	55.5
Males	141	44.5
Average Blood Pressure, Mm. Hg.		
Systolic	192	
Diastolic	114	
	Number	Percentage
Colored patients	150	47.4
White patients	167	52.6

RETINAL EXAMINATION

Each branch of the retinal artery was examined out to the finest terminals in each eye. If the vessels could not be seen because of cloudy media the patient was not included. It became obvious early in our experience that there were various degrees of arteriovenous nicking and the significance of the early changes was far different from that of the well developed lesion. We arbitrarily chose the following designations and recorded them as such on the patient's chart on the first examination: (1) early arteriovenous nicking, (2) moderate arteriovenous nicking and definite arteriovenous nicking (fig. 2). Later we found that Thiel, in Frankfort on the Main, recognized the vital necessity of making similar distinctions.

After one examines many retinal arteriovenous crossings it becomes clear that in the normal person there is no change in appearance of the veins at the crossing. In some cases the vein is slightly compressed or exhibits a U-shaped deformity caused by being pushed aside, but on close examination no area of obliteration of the vein is visible on either

side of the artery (fig. 2*B*). We have designated this lesion early arteriovenous nicking. It may be found in patients who never have had hypertension, but it is vastly more common in hypertensive than in nonhypertensive people; for this reason we suggest that it is an early stage in the development of definite arteriovenous nicking. We have observed such lesions develop in 1 patient, over a period of five years, into definite arteriovenous nicking.

Fully developed arteriovenous nicking is accompanied by complete obliteration of the vein on both sides of the artery and is easy to identify (fig. 2*A*). Partial obliteration of the vein or obliteration on only one side we termed moderate arteriovenous nicking. We have never seen such a lesion in nonhypertensive persons, but of course we cannot be as assured that it is pathognomonic of hypertension as we are that definite arteriovenous nicking is. We take this occasion to warn that crossings within one disk diameter of the optic disk must not be used, for not infrequently the vein dips deep into the retina in this region and gives the appearance of arteriovenous nicking. We have seen the latter phenomenon in many normal persons.

DETERMINATION OF THE SIZE OF THE HEART

Teleroentgenograms were made for every patient and the shape of the heart was carefully considered, but since the latter is not amenable to exact measurement we relied largely on comparison of the transverse diameter of the heart with the predicted transverse diameter from the tables of Ungerleider and Clark. These predictions are based on height and weight. We also determined the predicted transverse diameters by the tables of Hodges and Eyster, using the monogram in the book by Kurtz entitled "Orthodiascopy."[7] The predicted figures in these two sets of tables are much alike, but in this study we are reporting only on the figures from Ungerleider and Clark. We also measured the cardiothoracic ratio.

In his recent report Hodges[8] makes it clear that there is no accurate way to measure precisely the size of the heart, nor within narrow limits to determine the presence of enlargement, but if broader limits are allowed a reasonable degree of certainty of enlargement can be attained. It has for years been recognized that the cardiothoracic ratio is not a reliable index of enlargement (Kurtz). If the usual figure of 50 per cent is taken as the criterion of enlargement, one will miss many hearts that are definitely enlarged, but if a heart attains this rather considerable transverse diameter there is hardly any doubt that it is enlarged, unless the heart is clearly lying transversely above a definitely high diaphragm. For this reason we adopted this figure as one of our criteria of enlargement. In order to detect those enlarged hearts which had not yet attained a cardiothoracic ratio of 50 per cent we used the prediction tables of Ungerleider and Clark.[9]

7. Kurtz, C. M.: Orthodiascopy, New York, The Macmillan Company, 1937.

8. Hodges, F. J.: Determination of Heart Size, Am. J. Roentgenol. **42**:1 (July) 1939.

9. Ungerleider, H. E., and Clark, C. P.: A Study of the Transverse Diameter of the Heart Silhouette with Prediction Table Based on Teleroentgenogram, Proc. A. Life Insur. M. Dir. America (1938) **25**:84, 1939.

We did not consider a heart enlarged unless the transverse diameter was 10 per cent greater than the predicted value.[10] A study of 137 normal controls showed this to be a satisfactory standard.

RESULTS

There were 148 patients among the 317 studied who had definite arteriovenous nicking (table 2), and 142 (or 96 per cent) of the 148 had enlargement of the heart (a cardiothoracic ratio of 50 per cent or above or a heart diameter 10 per cent above the predicted transverse value). We are unable to learn why the other 6 patients did not have enlargement of the heart. In looking over the teleroentgenograms of this group we did not find a single one in which any good clinician would not have considered the heart enlarged, even without the formality of measurement. We may say, then, with only slight possibility of error, that definite arteriovenous nicking will be accompanied by enlargement of the heart; this is true even if the blood pressure is normal at the time of the examination, which it often is. We may also say that if the patient has definite arteriovenous nicking and enlargement of the heart is found, the enlargement is primarily due to hypertension.

We may properly speculate, if enlargement of the heart is almost always found in the presence of arteriovenous nicking, which comes first. In order to throw some light on this, we studied the incidence of enlargement of the heart (using the aforementioned criteria) in 74 hypertensive patients without arteriovenous nicking. Of these, 23 (31 per cent) had enlarged hearts (table 3). This would seem to be a rather high incidence of enlargement of the heart to be compatible with the idea that the two conditions appear about the same time.

It is apparent that in most cases enlargement of the heart takes place before arteriovenous nicking, though we had 6 patients (out of 148) for whom the reverse was true. If patients with severe coronary arterial (proved clinically and electrocardiographically) syphilitic or rheumatic lesions of the heart are excluded from the group of hypertensive patients

10. Orthodiascopy was not employed, as we thought this method had little or no advantage over the teleroentgenographic and is subject to many more errors in technic. The great error in measuring the heart size is due to the fact that one is unable to measure the volume of the heart during life. Unhappily, late antemortem and early postmortem changes prevent one from determining accurate heart size even at necropsy. Orthodiascopy, as well as teleroentgenography, is subject to this great error; so the possible advantages of this method, even in the hands of the keenest technicians, are slight indeed. During the course of this study we wrote to the cardiologists in fourteen of the leading medical schools of the United States. Of the twelve that gave answers, seven still use cardiothoracic ratios, four use orthodiascopy and five use teleroentgenograms with prediction tables to determine the expected transverse diameters. Those using cardiothoracic ratios indicated that they did so out of indifference to the problem of early changes in heart size. This seems a deplorable state, as all recent studies have shown the fallibility of this method.

without arteriovenous nicking, enlargement of the heart is found in only 5 cases (6.7 per cent). However, there is no point in trying to exclude patients with coronary heart disease from a group of those with hypertension. The two diseases are constant partners in the destruction of man. But this knowledge forces one to be on guard for other lesions when an enlarged heart is discovered in a hypertensive patient and search of the retinal arteries fails to reveal arteriovenous nicking.

This knowledge has been of great clinical value to us in relation to all forms of heart disease, for hypertension occurs frequently with other diseases of the heart, such as chronic coronary arterial, syphilitic or rheumatic heart disease, and it is valuable to have some method of

TABLE 2.—*Incidence of Arteriovenous Nicking With and Without Associated Enlargement of the Heart* *

	Number of Patients	Percentage
Nicking present, heart enlarged	142	95.7
Nicking present, heart normal in size	6	4.3

* The criterion of enlargement was a cardiothoracic ratio of 50 per cent or above or a heart diameter 10 per cent above the size predicted according to the tables of Hodges and Eyster.

TABLE 3.—*Relation of Absence of Arteriovenous Nicking to Enlargement of the Heart* *

	Number of Patients	Percentage
Nicking absent, heart enlarged	23	31
Nicking absent, heart normal in size	51	69

* The criterion of enlargement was a cardiothoracic ratio of 50 per cent or above or a heart diameter 10 per cent above the size predicted according to the tables of Hodges and Eyster.

recognizing the importance of the factor of hypertension. This has become so important to us that we begin all cardiac examinations by a retinal study.

We have applied these same statistical analyses to the other two groups of patients, those with early arteriovenous nicking and those with moderate arteriovenous nicking (table 4). It is obvious that early arteriovenous nicking has no relation to the size of the heart, since less than half (41 per cent) of these patients had enlargement of the heart. However, moderate arteriovenous nicking is almost as valuable an index as definite arteriovenous nicking, since 86.3 per cent of this group had enlarged hearts. As a matter of interest we have combined these figures in table 5, in order to show the distribution of the retinal arterial changes in the patients with enlarged hearts and the distribution of such retinal

changes in patients with hearts of normal size. It is worth while to point out that among the patients with enlarged hearts arteriovenous nicking was absent or in an early state in only 19 per cent, whereas definite or moderate nicking occurred in 81 per cent. Now, in the group with hearts of normal size (table 6), 88 per cent had either normal crossings or only an early degree of arteriovenous nicking, whereas in only 12 per cent was the nicking moderate or definite. If all patients with serious coronary arterial disease were eliminated these totals would of course be much more striking.

TABLE 4.—*Incidence of Early and Moderate Degrees of Arteriovenous Nicking With and Without Associated Enlargement of the Heart*

	Number of Patients	Percentage
Early arteriovenous nicking	43	
Heart enlarged	18	41.9
Heart normal in size	25	58.1
Moderate arteriovenous nicking	51	
Heart enlarged	44	86.3
Heart normal in size	7	13.7

TABLE 5.—*Incidence of Arteriovenous Nicking in Two Hundred and Thirty-Three Patients with Enlarged Hearts and Eighty-Three Patients with Hearts of Normal Size*

	Degree of Nicking	Number of Patients	Percentage
Heart enlarged		233	
	None	26	11.2
	Early	18	7.7
	Moderate	44	18.9
	Definite	145	62.2
Heart normal in size		83	
	None	48	57.8
	Early	25	30.1
	Moderate	7	8.5
	Definite	3	3.6

RELATION OF ARTERIOVENOUS NICKING TO RENAL FAILURE

It is impractical to measure renal function accurately for clinic patients, so we were unable to determine precisely the relation between degrees of retinal arterial change and the amount of renal damage present, but we can say positively that in every instance in our series arteriovenous nicking occurred before permanent renal failure in patients with benign essential hypertension. Therefore, if one encounters a patient with permanent renal failure in whom arteriovenous nicking is absent one can be reasonably sure that he is suffering from some other form of nephritis than that due to late benign essential hypertension. Renal failure may occur too quickly in a case of malignant hypertension

to allow development of arteriovenous nicking. We may say, then, that arteriovenous nicking is a useful sign in the differential diagnosis of chronic nephritis associated with late stages of benign essential hypertension and chronic glomerulonephritis, malignant hypertension or other forms of renal disease.

SUMMARY AND CONCLUSIONS

We were able to show by this study of 317 patients with hypertension that retinal arteriovenous nicking is so closely related to enlargement of the heart that if this lesion is found we may expect to find an enlarged heart. Furthermore, if this lesion is found in a patient with enlargement of the heart, the latter condition can be accounted for by hypertension, even if the blood pressure is normal at the time of examination. We may also state that if the heart of a hypertensive patient is enlarged and no arteriovenous nicking is found, the enlargement is not likely to be due to hypertension alone and a careful search for other lesions, such as those of severe coronary arterial disease, syphilis or rheumatic fever, is clearly indicated.

There is apparently no relation between the early change in the retinal arteries, which we have designated early arteriovenous nicking, and enlargement of the heart, but the later change, which we have called moderate arteriovenous nicking, is definitely related to enlargement of the heart, though not so closely as the fully developed lesion (definite arteriovenous nicking).

Arteriovenous nicking is important in the differentiation of the chronic nephritis associated with late hypertension and chronic glomerulonephritis.

It is hoped that this study will help to show the importance of careful observation of the changes in the retinal vessels and the necessity for more accurate description. We see too many reports, even from the best institutions, in which retinal arteriosclerosis is evaluated as 4 plus or grade 3 but the lesions are not described. Such a notation is meaningless. It is much more valuable to state whether arteriovenous nicking, extremely narrow arteries, changes in the caliber in arteries, etc., are present.

FIBER DISSOCIATION IN PERIPHERAL NEUROPATHY

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The various functions of the peripheral nerve are not uniformly affected in the peripheral neuropathy accompanying alcoholism and other conditions leading to disturbed nutrition. With regard to sensation, it has been observed that modalities which are eventually to be carried in the posterior columns, and which are newer in the developmental (phylogenetic) scale, are likely to be impaired earlier and more severely. Neurologic textbooks[1] note that light touch, position and vibration senses are relatively severely affected, while pain sense may be either fairly well preserved or, more commonly, preserved in a "paradoxic" form.

In this paper we have attempted to correlate these observations with certain experimental, clinical and metabolic data.

FIBER TYPES

The most extensive attempt to group fibers in the peripheral nerves on a functional basis was that of Head,[2] who divided sensation into the following types:

1. Epicritic sensation: This includes light touch sensation over hairless parts, cutaneous localization, two point discrimination, discrimination of size and discrimination of temperatures between 26 and 38 C.

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1. (*a*) Gowers, W. R.: A Manual of Diseases of the Nervous System, Philadelphia, P. Blakiston, Son & Co., 1888. (*b*) Grinker, R. R.: Neurology, ed. 2, Springfield, Ill., Charles C. Thomas, Publisher, 1937. (*c*) Wechsler, I. S.: A Textbook of Clinical Neurology, ed. 2, Philadelphia, W. B. Saunders Company, 1932. (*d*) Brain, R.: Diseases of the Nervous System, New York, Oxford University Press, 1933.

2. Head, H.: Studies in Neurology, New York, Oxford University Press, 1920, vol. 2.

2. Protopathic sensation: This includes cutaneous pain, pain due to physical factors or to hair plucking and discrimination of temperature in extreme ranges.

3. Deep sensation: This includes recognition of pressure, pain due to excessive pressure, recognition of muscle movement, localization of application of pressure and recognition of joint motion due to passive movement.

Head expressed the belief that in the cord itself a regrouping of these three main streams occurs. All impulses for pain (both deep and superficial) and for temperature discrimination (both epicritic and protopathic) travel together. Touch impulses, however, may traverse more than one path in the cord. Head stated the belief that the spinal cord is the site of most of the transmutation to the secondary level of sensation. This involves a regrouping of impulses into specific sensory groups, as well as separation of afferent sensory and nonsensory (coordinating) impulses.

Head had no evidence available, however, to show that functional differentiation in the peripheral nerve could be correlated with anatomic variations in fibers or with the speed of transmission of impulses, but this gap in knowledge has been filled by Gasser and his associates.[3]

The latter authors recorded the grouping of fibers in the isolated sensory nerve by studying the action potential waves obtained by direct electrical stimulation at various strengths. As the strength of the stimulus was increased, three distinct groups of waves were obtained, the first with relatively light shocks, the second when the stimulus was increased to ten times the original threshold and the third only after the stimulus reached a level one hundred times the original threshold, and then only after a perceptible delay. The waves were labeled the A, B and C waves, respectively, and the fibers transmitting each were similarly designated. The authors, using the saphenous nerve of the cat, then measured the speed at which these waves travel. The A waves are transmitted at a speed of 30 to 75 meters per second, the B waves at the rate of 15 to 25 meters per second and the C waves at the relatively slow rate of 1 to 2 meters per second, which accounts for the delay in their appearance.[4]

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3. (*a*) Gasser, H. S.: Conduction in Nerves, in Relation to Fiber Types, A. Research Nerv. & Ment. Dis., Proc. **15**:35, 1935. (*b*) Clark, D.; Hughes, J., and Gasser, H. S.: Afferent Function in the Group of Nerve Fibers of the Slowest Conduction Velocity, Am. J. Physiol. **114**:69, 1935.

4. The terminology here presented is that given by Gasser, in 1935, and we have continued to use it throughout this paper for purposes of simplicity. Subsequently, however, Erlanger and Gasser (Electrical Signs of Nervous Activity, Philadelphia, University of Pennsylvania Press, 1937) preferred to consider the B elevation

(Footnote continued on next page)

It has been previously noted that within a group the speed of the impulse is proportional to the diameter of the fiber. This is not strictly true for fibers of different structural and electrophysiologic qualities, but it is important for our purposes that the C waves have been found to be transmitted by the unmyelinated fibers of very small diameter.[5] The A waves travel in a group of large myelinated fibers and the B waves in a group of smaller myelinated fibers with slightly different qualities.

Several attempts have been made to determine the function of fiber groups and to correlate fiber size with sensory modalities. Heinbecker, Bishop and O'Leary [6] stimulated electrically the proximal end of an exposed nerve in a human amputation stump. The largest and most irritable fibers were found to transmit touch impulses, but a slightly stronger stimulus, still insufficient to produce C waves, produced pain. This indicates clearly that certain pain impulses are carried in fibers other than C fibers.

Clark, Hughes and Gasser [3b] showed by progressive increases in electrical stimulation of the saphenous nerve of the anesthetized cat that at the exact point at which the stimulus became sufficiently strong to cause the appearance of C waves marked augmentation of the respiratory and circulatory reflexes occurred. This indicated to the investigators that the C fibers (1) carried afferent impulses and (2) transmitted pain.

Furthermore, cocaine block of the peripheral nerve (in the dog) was found to cause initial disappearance of the C waves, followed later by falling out of the A and B waves, an indication that cocaine blocks the smallest fibers first and the largest last. In man the order in which the various sensory modalities disappear is that of cold, warmth, pain and pressure.[3a] Assuming that in man the largest fibers are similarly most resistant to cocaine, it may be inferred that in the sensory nerve the largest fibers carry sensations of pressure, since these are affected last. The largest fibers which carry sensations of pain must be somewhat smaller than these.

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of the electroneurogram of the saphenous nerve as a subdivision (delta) of the A fibers. They confined the B elevation to the activity which appears in the fastest fibers in the gray rami and which does not occur in the sensory nerve. The A and C fibers mediate both sensory and motor activity (Grundfest, H.: Bioelectric Potentials, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Stanford University Press, 1940, vol. 2, p. 213). In the latter classification, the B fibers are known to occur only in the preganglionic nerves of the autonomic system and probably also in the postganglionic fibers of the ciliary nerve (Grundfest, H.: Properties of Mammalian B Fibers, Am. J. Physiol. **127**:252, 1939). An excellent experimental survey of this entire problem has recently been made by Zotterman (Touch, Pain and Tickling, J. Physiol. **95**:1,1939).

5. Ranson, S. W., cited by Gasser.[3a]

6. Heinbecker, P.; Bishop, G. H., and O'Leary, J.: Pain and Touch Fibers in Peripheral Nerves, Arch. Neurol. & Psychiat. **29**:771 (April) 1933.

On the other hand, when isolated cat nerve is rendered ischemic by a pneumatic cuff,[3a] the larger A and B fibers are the first to be completely blocked. At this point, a "considerable fraction of the C fibers are still found to be functioning; and stimulation of these produces reflex effects." The same result is obtained whether the sphygmomanometer cuff is applied to the whole limb or whether pressure is applied directly to the nerve trunk, the effect being interpreted as the result of local ischemia of the nerve trunk itself.[7]

THE DOUBLE PAIN RESPONSE

The experiments just described indicate that pain sensation is carried both by fast and by slow fibers. This requires some explanation. It has been recognized for some time [8] that a single pinprick of moderate intensity applied to the skin of the arm or leg results in two sensations. The first can be detected almost immediately after the stimulus as a localized, distinct, not unpleasant prick. The second is more diffuse, and if the stimulus is at all intense, the sensation is unpleasant and somewhat prolonged.

Lewis and Pochin [8] by the use of cocaine were able to eliminate the second response while the first was still perceptible, and by asphyxia to eliminate the first response while the second was still preserved. They measured the time necessary for the second response to be perceived and found the delay to be 2.0 seconds from the toe, 1.1 seconds from the knee and 0.8 seconds from the thigh. The difference was evidently a reflection of the time necessary for transmission of the impulse along the nerve fibers at a relatively slow rate and was in proportion to the distance traveled.

They concluded, therefore, that the sensation of pain is transmitted by two sets of fibers, a fast group (A and B) and a slow group (C). The velocity of transmission along fibers of the C group (1 to 2 meters per second) accounts satisfactorily for the delay and would allow its prediction.

This work confirms the electrophysiologic observation that pain sense is carried by two distinct groups of fibers. In asphyxia of the sensory nerves, the same investigators [8] found that the defects in the senses of touch, cold, warmth and fast conducted pain begin almost simultaneously, while the defect in slowly conducted pain sense comes later and is preceded by an exaggerated pain response. Most of the sensory modalities decline slowly but are eliminated completely within a relatively short

7. Lewis, T., and Pochin, E. E.: The Effects of Asphyxia and Pressure on the Sensory Nerves of Man, Clin. Sc. **3**:141, 1938. Clark, Hughes and Gasser.[3b]

8. Lewis, T., and Pochin, E. E.: The Double Pain Response of the Human Skin to a Single Stimulus, Clin. Sc. **3**:67, 1937.

period of each other. Touch sense, however, may be lost early. In general, no precise relation between the falling out of specific modalities and the fiber conduction rate can be demonstrated except the constant preservation of the sense of slowly conducted pain (C fibers) well beyond the time of falling out of sensations of touch, vibration, joint position and rapidly conducted pain (A and B fibers). In short, pain sense persists after other sensations have been lost. Just before the onset of complete analgesia this second pain response becomes most intense and conspicuously long lasting.

Local chilling of a peripheral nerve trunk causes the dropping out of functions in an order somewhat different from that observed with asphyxia. Here too, however, delayed pain sense is retained after most other modalities have been lost, and again marked hyperalgesia occurs.[9]

These observations are also confirmed by the results of the in vitro studies of Gerard.[10] He observed that when nerves are subjected to anoxia in a closed chamber fibers are not blocked in a homogeneous or continuous fashion but fall out in groups, in an order probably determined by fiber diameter. In this type of experiment the block occurs first in groups which have a higher rate of metabolism. Replacement of the fluid in which the fibers are bathed has no effect in preventing or delaying block. This indicates that block is due to exhaustion of an oxidizing reserve and militates against the supposition that it is due to the accumulation of metabolites. This principle is of considerable importance in the interpretation of in vivo asphyxia experiments. In conjunction with Bickford's work (production of hyperalgesia without the factor of impeded blood flow), it offers an explanation of the sensory phenomena independent of humoral mechanisms.

PLANTAR DYSESTHESIA

Plantar dysesthesia is a term which we have applied to an abnormal sensitivity of the sole of the foot to scraping. It has been variously called "hyperalgesia," [2] "paradoxic pain" [1d] and "plantar hyperesthesia."[11] This phenomenon is common in cases of partial damage to the peripheral nerves [2] and of the peripheral neuropathy accompanying alcoholism.[12] Beyond noting its presence, clinicians have been little concerned with its physiologic importance.

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9. Bickford, R. G.: The Fiber Dissociation Produced by Cooling Human Nerves, Clin. Sc. **4**: 159, 1939.

10. Gerard, R. W.: Response of Nerve to Oxygen Lack, Am. J. Physiol. **92**: 498, 1930.

11. Jolliffe, N.: Diagnosis, Treatment and Prevention of Vitamin B_1 Deficiency, Bull. New York Acad. Med. **15**:469, 1939.

12. Brain.[1d] Jolliffe.[11]

Head suggested that this type of sensation, although exaggerated, need not be irritative in origin but might well be the expression of an actual deficiency of function. He implied that certain afferent (epicritic) impulses may exert an inhibitory effect on other (protopathic) impulses.

> The condition known as protopathic sensibility arising from lesions of the peripheral nerves is characterized by an overresponse to painful and to thermal cutaneous stimuli. This overresponse is due to the uncontrolled action, on normal sensory centers, of impulses capable of exciting sensations heavily charged with feeling-tone.[2]

Rivers and Head [2] pertinently suggested that the cornea (inadequately supplied with touch fibers) is exquisitely sensitive. Lewis and Pochin [13] (in asphyxia) also noted exaggeration of the second pain response, with the progressive loss of other sensory modalities.

A possible modus operandi has been suggested by Gasser [14]: "It is quite possible that the function of impulses which run on ahead of the others is to adjust the excitability of the synapse in preparation for the arrival of later impulses."

One may speculate that normally most of the blow is cushioned by the previous preparation of the synapse by early arriving impulses. When the fast fibers are blocked, the force of the impulses transmitted by the slow fibers is allowed to pass undamped, and the result is a rush of unpleasant feelings, which may occur after an apparent delay in perception. It seems plausible, therefore, to account for the hyperalgesia, or dysesthesia, which occurs in the course of asphyxial block by interpreting it as the result of impulses which have traveled along slowly conducting fibers, reaching synapses not properly inhibited by rapidly traveling impulses. The uninhibited impulse is thus perceived at an intensity much greater than normal.

Furthermore, this phenomenon is not confined to lesions of the peripheral nerves. Dysesthesia has classically been associated with lesions in the region of the thalamus. In cases of such lesions, Head [2] described the response to pinprick as slow and persisting long after stimulation had ceased. His patients described the sensation experienced when the tips of the fingers were drawn over the affected sole as follows: "It's burning, as if you were tearing the skin off" and "like nails digging into the flesh." These responses bear a striking similarity to those elicited from persons with the peripheral neuropathy accompanying alcoholism or from patients in whom dysesthesia has been produced by asphyxia of a limb (see "Experimental Study"). In addition, the threshold for simple pinprick is high in all three conditions. Head

13. Lewis and Pochin (footnotes 7 and 8).

14. Gasser, H. S.: Control of Excitation in the Nervous System, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, p. 169.

mentioned that even the vibrating tuning fork may cause an unpleasant sensation in patients with the "thalamic syndrome." This, too, is a not infrequent observation in cases of the peripheral neuropathy of alcoholism. In general, Head asserted,[2] "a stronger prick and greater pressure are required to cause pain on the affected side, but when once evoked, the pain was much less bearable and produced a stronger reaction." In many cases the patient's reactions were delayed and explosive. The actual time, however, was not measured.

Head [2] expressed the belief that this state occurred as the result of interruption of impulses normally traveling from cortex to thalamus.

> The only function which can be ascribed to these corticothalamic paths is that through them the cerebral cortex controls, in some way, the activity of the thalamus. If this view is correct, lesions which interrupt these paths, but leave intact the main substance of the optic thalamus, must lead to a permanent overactivity of functions exercised by that organ.

This inhibitory mechanism is similar to that postulated for the peripheral nerve. We wish, furthermore, to emphasize the clinical similarity.

Less well known is the occurrence of a comparable phenomenon with lesions elsewhere in the central nervous system. Kendall [15] has reported 3 cases of disease of the brain stem in which delayed dysesthesia was present. The delay was of the same order as that observed with lesions of the peripheral nerves, namely, about 2 seconds. He postulated that the central nervous system must contain some system of fast and slow fibers similar to that described by Gasser for the peripheral nerves, with a corresponding inhibitory mechanism and timing arrangement.

SENSORY DISSOCIATION IN PERIPHERAL NEUROPATHY

Jolliffe [11] has described the order of development of sensory and motor defects in the peripheral neuropathy accompanying alcoholism as follows:

> Heaviness of the lower extremities, and calf muscle cramps are usually the first symptoms. These are followed by paresthesias in the toes and fingers, burning of the feet, and pain in the legs. It should be emphasized that pain, though nearly always present, can often be elicited only by a leading question. Calf muscle tenderness and plantar hyperesthesia are as a rule the earliest objective signs. The hyperesthesia may extend up the ankles and legs in a sock distribution. Vibratory sensation may be lost in the toes. These signs we classify as suggestive, and a positive diagnosis of polyneuritis is not made, as circulatory disturbances may cause these or very similar findings. When, however, in addition to these signs, the ankle jerks are absent, a diagnosis of mild polyneuritis can be made. As the deficiency continues, the sensory and motor changes advance, the knee jerks disappear, position sense in the toes becomes impaired, atrophy of the calf muscles develops and foot drop follows.

15. Kendall, D.: Some Observations on Central Pain, Brain **62**:253, 1939.

Furthermore, plantar dysesthesia was a constant finding in 32 cases of acute neuropathy accompanying alcoholism,[16] but dysesthesia of the delayed type does not seem to have been studied as such in these cases.

SUMMARY OF LITERATURE

A review of the literature to date, therefore, reveals the following essential points:

1. There is good evidence that the sensory peripheral nerve carries three different types of fibers. These vary in size, in irritability and in speed of impulses. The smallest, denoted by Gasser as C fibers, are nonmedullated, are least irritable, are smallest in diameter and transmit impulses at a speed far lower than that of the others. The faster conducting fibers, which are medullated, are known as the A and B fibers.

2. With regard to the functions of the various types of fibers, Gasser [14] concluded:

> The fastest fibers carry touch impulses but not pain, and the C fibers carry pain, without touch or pressure. However, pain is also found in the second elevation (B) and overlaps warmth and probably pressure. . . . There must be some other reason than the modalities of sensation for the numerous velocities.

3. When fibers are blocked by asphyxia, the C fibers continue to function for some time after the A and B groups have been completely blocked.

4. In contrast, when the fibers are subjected to the action of a local anesthetic, such as cocaine, the C fibers are the first to be blocked.

5. The sensation carried by the C fibers has been identified with delayed pain.

6. The presence of double pain sensation has been demonstrated under normal conditions. The delay in perceiving "second pain" has been shown to be of the order of magnitude which would be expected if the sensation were transmitted by the C fibers.

7. When asphyxia results in the loss of sensations carried in the larger fibers "second pain" is not only preserved but becomes distorted and unpleasant. The threshold for pain perception, however, becomes high.

8. The phenomenon of delayed plantar dysesthesia appears to be the result of the continuing transmission of impulses along the C fibers, while all the faster (A and B) fibers have been blocked. It seems

16. Goodhart, R., and Jolliffe, N.: Effects of Vitamin (B_1) Therapy on the Polyneuritis of Alcohol Addicts, J. A. M. A. **110**:414 (Feb. 5) 1938. Jolliffe, N.; Colbert, C. N., and Joffe, P. M.: Observations on the Etiologic Relationship of Vitamin B (B_1) to Polyneuritis in the Alcohol Addict, Am. J. M. Sc. **191**:515, 1936.

possible that the fast (A and B) fibers raise the threshold of the sensory synapse in the dorsal gray matter for the reception of later and slower impulses (C fibers). With asphyxiation and the falling out of the fast (A and B) fibers, this normal preparation of the synapse does not occur. At this point sensation is perceived in an exaggerated and abnormal fashion.

EXPERIMENTAL STUDY

The loss of function in a limb which is subjected to acute anoxia was studied in 10 subjects free of disease affecting the peripheral nerves. We employed the technic previously described by Clark, Hughes and Gasser [3b] and Lewis and Pochin,[7] using the leg rather than the arm. The blood supply to the leg was interrupted by means of a blood pressure cuff applied above the knee and inflated to a pressure well above the systolic (190 to 210 mm. of mercury).

We followed the progress of defects in light touch and superficial pain sense, vibratory sensation in the toes, toe position sense, the achilles tendon reflex, strength of dorsiflexion of the toes, plantar sensation (scraping) and reaction time for the plantar sensation. In a number of cases the cold and warmth sensations were also tested.

The nature of the experiment required frequent testing. The number of functions tested for was therefore limited, and the time intervals between tests were kept at five to seven minutes to avoid excessive fatigue. For the same reason, relatively gross methods of testing (such as those employed in clinical examinations) were used. We believe our observations are experimentally valid because we always had the other, normal leg for comparison. This made it possible to detect defects much earlier than would otherwise have been possible.

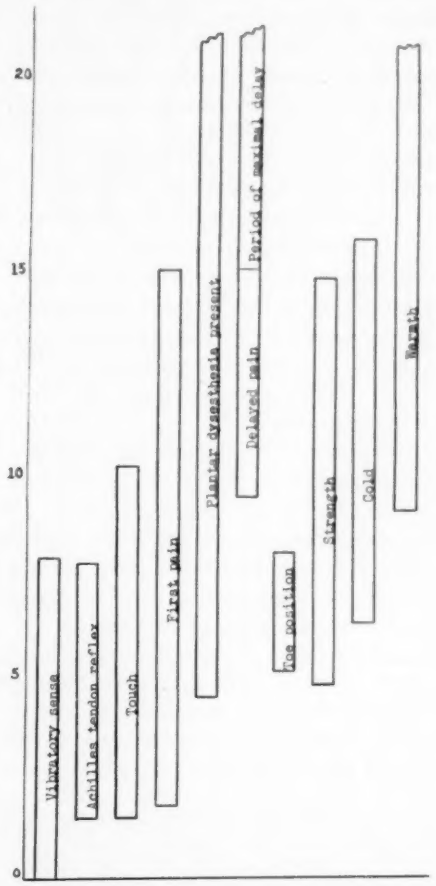
The results, in general, agree with those of the aforementioned experimenters. The accompanying graph indicates the appearance of sensory defects in the 10 subjects studied by this method. While there was a good deal of variation from case to case in the precise time of appearance of individual defects, several features which we believe to be of significance were common to all.

1. Touch and vibratory senses were always affected early, as compared with pain or position sense. Depression of the ankle jerk followed closely on the impairment of touch and vibratory sense.

2. Superficial pain sense was affected shortly after the earliest defects appeared, but was practically never lost first.

3. Position sense, while affected late, nevertheless was one of the functions complete loss of which occurred earliest. Once a defect in position sense could be detected, complete loss was sure to follow within a few minutes. This probably means that early changes in this function cannot be detected by the present clinical methods.

4. Pain sense was never completely lost. After some time the threshold became high and the sensation delayed. We have arbitrarily chosen this point to represent the complete loss of "first pain." We reached this figure by noting the time at which the delay in pain trans



The loss of function in a foot subjected to interruption of the blood supply. The base line (*O*) is the point at which the first defect in vibratory sense could be detected. The left border of each bar indicates the first point at which the defect in a given sense could be detected. The right border indicates the first point at which the function was entirely lost. A jagged right border denotes persistence of the function past the point at which the experiment was terminated. The results represent the average values for 9 or 10 patients.

mission reached its maximum. It seems probable that only at this point have all the fast pain fibers been blocked. Furthermore, our figures are in substantial agreement with the observations of Lewis and Pochin.

5. Plantar dysesthesia developed in every case. There is some question in our minds how this sensation (which in every case became delayed) should be classified, but it is undoubtedly closely allied to pain. It was unpleasant in every case but 1 and was usually described as a combination of burning and pain. Typical descriptions of the sensation stated it was "as though my foot was on a hot steam pipe," "like burning and electric shock" and "as though it was cut and was bleeding." When plantar dysesthesia was evident, a pinprick on the dorsum of the foot was felt as delayed, prolonged burning. It was, in any case, a sensation which was never felt in the normal, control foot under similar stimulation.

6. From the time of its appearance, the threshold for producing this sensation was in general rather high. Occasionally, however, a finger drawn along the patient's sole was sufficient to elicit it. Under the latter circumstances, a further period of anoxia required relatively firm scraping with a hard blunt object (such as the handle of a reflex hammer) to produce the sensation.

Delay occurred eventually in every case. When it first appeared, the time necessary for the patient to react to the stimulus was barely more than the reaction time for the opposite, normal side. With prolonged ischemia, further increase was evident, the rate of increase approaching a final limiting value (0.9 to 1.7 seconds).[17]

7. The earliest changes in superficial sensation occurred in each case over the inner and the dorsal surface of the great toe. This area and a few square centimeters behind and laterally were used for repeated testing. In the case of superficial pain, it was necessary to confine testing to localizable pain spots, as some areas of skin seemed to have lost their capacity to transmit pain, while others were still able to do so to some extent.

17. The measurement of delay was performed as follows: At the beginning of the experiment the patient was required to give a signal as soon as he felt the prick of a pin on the lower part of his foot. The interval between the stimulus and the signal was timed with a stopwatch six or eight times for each foot. The last four or six values, if reasonably close to each other, were averaged to obtain the base reaction time. At intervals throughout the experiment the pinprick reaction time was remeasured for both feet. In every case it was constant on the control side. When the value had reached a maximum on the anoxic side and showed no further increase with successive observations, four to six values were again averaged. The figure thus obtained was considered the average total delayed reaction time. The base reaction time was then subtracted from this to give the final value for delay. This method is admittedly approximate, but since we were interested in the fact that delay occurred and became constant, rather than in its accurate measurement, we deemed the method sufficiently exact for our purposes.

8. The precise observation of defects in the sensations of heat and cold offered some difficulties, and these modalities were completely tested in only 7 patients.[18] The defects in sensation of cold appeared relatively late, and sensation was lost at about the same time that "first pain" had disappeared and delay had become maximal. Perceptible defects in the sensation of warmth appeared extremely late. As a rule, these occurred about the time that touch and vibration senses had completely disappeared. When sensation of pain became delayed, the perception of warmth was generally noted to be similarly delayed in reaching consciousness. The detection of warmth was never completely lost during the period of the experiment, a property which was shared with delayed dysesthesia. This may indicate that pain and warmth impulses travel along similar pathways in the peripheral nerve.

9. At approximately the time of appearance of plantar dysesthesia the power of dorsiflexion of the great toe became impaired. Complete paralysis generally coincided with the appearance of maximal delay in plantar dysesthesia and pain transmission.

10. With the onset of delayed dysesthesia a good deal of local discomfort occurred. The sensation was difficult to describe but was called "tightness" or "a pain" or "just an uncomfortable feeling."

11. The base line used for the chart represents the time at which vibratory sense first became perceptibly impaired. In each case the time was measured from this point. This value was used, rather than the total period of anoxia, because of the tremendous variation in the time (eight and a half to twenty-four minutes) necessary for the first defect to appear. Once this point was reached, the rate of progression of defects varied little among different subjects.

In order to examine further the variation in the length of the anoxic period necessary for defects to appear, we repeated the same experiment on a number of patients with peripheral neuropathy. Despite the preexistent defects in the peripheral nerve, the further impairment of function took just as long to become manifest as in the average person without peripheral neuropathy.

We may infer, therefore, that the time necessary for the appearance of the first sign of defective sensation is not an index of any fundamental property of the state of the nerve itself, but rather is a reflection of the nutritional reserve supply. These observations are consistent with those of Gerard [10] on the isolated nerve.

12. Vasomotor changes were not observed in detail. After a short period of anoxia vasodilatation was manifested by the mottled cyanosis which is generally associated with clinical occlusion of the vessels of the

18. The instruments used in stimulation were metal test tubes, 1 cm. in diameter, containing water at a temperature of 10 to 15 or 55 to 65 C.

leg. When the cuff was deflated, there was marked bright pink flushing of the leg, again indicating vasodilatation.

13. The changes were completely reversible. Within 30 seconds of deflation of the cuff, peripheral nerve function had returned almost to normal. It did, however, take 2 to 4 minutes for the complete return of vibratory and light touch sensation. These, it will be recalled, were the first to disappear. In every case, testing at the end of 2 minutes showed some return of the ankle jerk, and at 4 minutes it had returned to normal. There was some discomfort of the "pins and needles" type, which lasted for about 5 minutes. Because of the rapidity of the changes following restoration of the circulation, it was impossible to follow in any greater detail the order of return of function.

CLINICAL DATA

In order to illustrate more fully the similarity of the neurologic changes in anoxia to those resulting from the peripheral neuropathy accompanying chronic alcoholism, 2 cases are briefly described.

CASE 1.—*Vascular Occlusion, Femoral Artery.*—C. S., a 68 year old white housewife, entered Bellevue Hospital on Oct. 10, 1940 with hypertensive cardiovascular disease, auricular fibrillation and moderately severe cardiac failure. There was evidence of peripheral arteriosclerosis. No pulse could be felt in either foot, but there was no evidence of frank vascular insufficiency of the extremities.

The next day she complained of pain in the right foot, but it was not until two days later that the lower part of the leg was observed to be cold and cyanotic up to about the knee. A history of previous intermittent claudication was elicited at this time. On October 17 examination revealed signs typical of arterial occlusion of the right leg. The extremity was cold up to the knee and was cyanotic to a point 10 cm. below the knee. The pulse could be detected at the groin but not in the lower portion of the thigh, at the popliteal space or below. Lowering the leg resulted in rapid deepening of the cyanosis and severe pain in less than 2 minutes. Elevation caused blanching within a short period, which disappeared slowly when the leg was lowered to the bed. These changes were not present on the other side, where there were no signs of frank vascular insufficiency.

Neurologic Examination.—There was marked plantar dysesthesia of the involved foot, with a high threshold for scraping or superficial pain and a total delay of 2.0 to 2.2 seconds. When the sole was stroked, there was no reaction at all for 2 seconds. Suddenly the patient withdrew her leg, gave facial evidence of severe pain and wept. She described the sensation as unpleasant but was unable to give any further details. A similar phenomenon was evident in testing sensation with pinprick. A light pinprick was not felt at all. A slightly heavier stimulus was felt after 2 seconds as a diffuse, unpleasant burning.

Vibratory and position senses were absent in the toes, and touch sense was absent over the whole foot. The ankle jerk was absent. There was only slight ability to move the toes voluntarily. The calf muscles and the tibia were tender on pressure.

In contrast, the left leg revealed neither dysesthesia nor delayed sensation—pinprick or scraping being perceived within 1 second. There was no defect in sensibility to pinprick or in position sense, although there were slight loss of touch sense and some impairment of vibratory sense. The ankle jerk was absent. These

sensory changes were of the type frequently found in cases of arteriosclerosis of the extremities, without conspicuous circulatory impairment.

On the following day hemiplegia developed, and the patient died a few hours later.

Autopsy.—Multiple emboli were present, and the right femoral artery was completely occluded. On the left there was evidence of involvement of the vascular tree but no complete occlusion.

The similarity between these changes and those produced by experimental occlusion is apparent. We have since seen another case of embolization of the femoral artery, with similar sensory changes. In this case, collateral circulation was sufficient to allow complete reversal of the clinical signs and the disappearance of dysesthesia. This case completely confirms our experimental observations and indicates that the syndrome is completely reversible when the vascular supply is promptly reestablished.

CASE 2.—*Severe Peripheral Neuropathy Accompanying Alcoholism, with Vitamin Deficiency.*—H. O., a 42 year old man with chronic alcoholism and a history of prolonged dietary insufficiency, was admitted to the Psychiatric Division of Bellevue Hospital on Sept. 29, 1940, with evidences of moderate intellectual impairment. He was able, however, to cooperate exceedingly well for examination.

There was evidence of severe peripheral neuropathy, with bilateral foot drop, complete areflexia and atrophy and tenderness of the calf muscles.

Of particular note was the presence of severe plantar dysesthesia. The threshold was moderately high for touch and pinprick, but even relatively light stroking of the sole caused an unpleasant burning sensation, which was first observed 2 seconds after the stimulus. Pinprick was also delayed 2 seconds and was burning and unpleasant in character.

Although the sensation of superficial pain was defective only to a moderate degree, that of touch was severely impaired below the middle portion of the skin. Vibratory sense was markedly impaired in the shins and practically completely absent in the ankles and toes. Position sense was absent in the toes but present in the ankles. Sweating and cyanosis of both feet were present.

The upper extremities were similarly but somewhat less severely affected. There were bilateral wrist drop, areflexia and some wasting. When the palms of the hands were scraped with a blunt instrument the patient complained of an unpleasant burning sensation. Impairment of finger position sense, vibratory sense and sense of touch was severe, and that of sense of pain was moderate.

Chemical examination of the blood revealed a high fasting level of pyruvic acid. This metabolic defect has been shown by Bueding and Wortis [19] to be constantly associated with the peripheral neuropathy accompanying alcoholism.

Treatment with large doses of preparations of the vitamin B complex resulted in progressive improvement. After a month, there were some return of position and vibratory sense in the toes, complete absence of tenderness of the calf muscles and marked subsidence of plantar dysesthesia.

19. Bueding, E., and Wortis, H.: Pyruvic Acid in the Blood and Cerebrospinal Fluid, Proc. Soc. Exper. Biol. & Med. **44**:245, 1940. Wortis, H., and Bueding, E.: The Clinical Significance of Pyruvic Acid Content of the Blood and Cerebrospinal Fluid, Tr. Am. Neurol. A. **66**:90-94, 1940.

In summary, then, this patient with a severe vitamin B deficiency presented a neurologic picture similar to that in the preceding case, in which the disturbance was purely ischemic in nature, and to that in our cases of experimental ischemia. In the experimental cases, we were able to reverse the process by releasing the cuff. In 1 of our cases of embolism reversal occurred after reestablishment of the circulation. In case 2 reversal was accomplished by correction of the metabolic defect. We wish, furthermore, to stress the fact that this is not uncommon but is the usual picture in cases of the severe peripheral neuropathy accompanying alcoholism.

COMMENT

Three types of lesions affecting the peripheral nerve have been described:

In the first type, in which the lesion results from experimentally induced ischemia of a limb, fibers are blocked in groups in a more or less precise and predictable way, although all modalities cannot be sharply separated. Of importance is the fact that the smallest fibers carry "second pain" and that they are the slowest and the most resistant to anoxia. These facts explain the phenomenon of delayed dysesthesia, which occurred in every one of our cases of experimental anoxia.

The second type, in which ischemia occurs as the result of vascular occlusion of a pathologic nature, offers a striking resemblance to the first type. It seems justifiable to infer that the process is fundamentally the same. Here, again, the fibers have been blocked in essentially the same order, and the end result indicates the selective preservation of function in the group of small, slowly conducting C fibers. This is precisely what happened in our experimental subjects.

Finally, the peripheral neuropathy accompanying alcoholism, with nutritional deficiency, resembles the ischemic type in its fundamental features, namely, the early involvement of vibratory sense and loss of reflexes, the rarity of the complete loss of the sense of superficial pain, the almost invariable presence of plantar dysesthesia and the not uncommon phenomenon of delay in pain sensation and in plantar dysesthesia. Here, again, one may infer that the small, slowly conducting C fibers have retained their function after that of the larger and more rapidly conducting A and B fibers has been lost. Delay of 1 to 2 seconds implies almost complete blocking of the A and B fibers—at this point plantar dysesthesia is most marked. Delayed dysesthesia occurs only with severe involvement of the peripheral nerve.

This assumption is further confirmed by the pathologic observations of Greenfield and Carmichael.[20] They studied the peripheral nerves of patients with the peripheral neuropathy of alcoholism and of others with subacute combined sclerosis. They found that in both groups the

20. Greenfield, J. G., and Carmichael, E. A.: The Peripheral Nerves in Cases of Subacute Combined Degeneration of the Cord, Brain **58**:483, 1935.

number of large fibers in the peripheral nerves were significantly reduced in ratio and in number as compared with the normal. Swank,[21] studying pigeons which had been deprived of thiamine (vitamin B_1), so as to produce peripheral neuropathy, found that the large fibers appeared to suffer first and to the greatest extent. As the deficiency grew more marked, the medium-sized fibers were affected, but as a rule the smallest ones remained intact.[22] The resemblance of the changes associated with the peripheral neuropathy of alcoholism to those which result from asphyxia of any variety is an observation of more than purely theoretic interest. The former are now generally recognized as the result of a metabolic deficiency. The similarity between the clinical changes associated with this neuropathy and those encountered in cases of ischemia offers a physiologic explanation for the characteristic sensory dissociation seen in cases of the first-named condition.

SUMMARY

The effect of asphyxia on the function of the peripheral nerve has been studied and a characteristic order of loss of sensory modalities demonstrated which is in agreement with the observations of previous investigators.

The significance of the phenomenon of delayed plantar dysesthesia has been discussed, particularly its relation to the persistence of function in the small, slowly conducting, nonmedullated (C) fibers after the large (A and B) fibers have been blocked. We have speculated on the inhibitory function of the rapidly conducting fibers and the application of this mechanism to similar dysesthetic phenomena with lesions elsewhere in the nervous system.

The sensory changes associated with the peripheral neuropathy accompanying alcoholism have been compared with those which occur as the result of experimental or clinical occlusion of the blood supply to an extremity, in terms both of clinical resemblance and of similarities of damage to certain groups of nerve fibers. The significance of the resistance of the nonmedullated (C) fibers to certain metabolic factors (ischemia, avitaminosis) is emphasized.

This work suggests that those portions of the peripheral nerve which conduct impulses at higher rates of speed and which are most irritable have the highest metabolic requirements and are most susceptible to metabolic disturbances. Hence, in cases of avitaminosis or ischemia affecting the peripheral nerve the A and B fibers are most susceptible to damage.

21. Swank, R. L.: Avian Thiamin Deficiency, J. Exper. Med. **71**:683, 1940; personal communication to the authors, 1940.

22. This differs somewhat from the order of block due to asphyxia in vitro, in which fibers of medium size causing the second elevation are affected before the large ones. Again, however, small, slowly conducting nonmyelinated (C) fibers remain intact.

COCCIDIOIDAL ARTHRITIS

REPORT OF A CASE IN WHICH THE ANKLES WERE INVOLVED AND THE CONDITION WAS UNAFFECTED BY SULFANILAMIDE AND ROENTGEN THERAPY

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In 1931 a bulletin was published under the auspices of the California Department of Public Health in which the subject of infection with the fungus Coccidioides immitis was reviewed.[1] This bulletin was documented with 172 references and indicated that 286 instances of the disease among human beings had been observed up to that time. By 1938 Dickson and Gifford [2] reported that 495 instances of the disease had been observed in California alone and that the disease had caused 249 deaths. Up to the time of writing (April 1941), 19 additional reports concerning this disease have been listed in the *Quarterly Cumulative Index Medicus*.

Despite this large number of reported cases of coccidioidomycosis and the extensive literature concerning it, only 3 instances of the disease have been recognized at the Mayo Clinic. In the first case, reported by Foley, Love, Broders and Heilman,[3] the patient had coccidioidal osteomyelitis of the skull. In the second case, reported by Craig and Dockerty,[4] the patient had pulmonary and meningeal lesions. In the

From the Section on Surgical Pathology (Dr. Dockerty) and the Section on Orthopedic Surgery (Dr. Meyerding), the Mayo Clinic.

1. Coccidioidal Granuloma, Special Bulletin 57, State of California Department of Public Health, June 1931.

2. Dickson, E. C., and Gifford, M. A.: Coccidioides Infection (Coccidioidomycosis): II. The Primary Type of Infection, Arch. Int. Med. **62**:853-871 (Nov.) 1938.

3. Foley, M. P.; Love, J. G.; Broders, A. C., and Heilman, F. R.: Coccidioidal granuloma: Report of a Case Originating in Texas, West. J. Surg. **48**:738-741 (Dec.) 1940.

4. Craig, W. M., and Dockerty, M. B.: Coccidioidal Granuloma: A Brief Review with Report of a Case of Meningeal Involvement, Minnesota Med. **24**: 150-154 (March) 1941.

third case, reported in this paper, the patient had coccidioidomycosis of the ankle joints.

The reason for the extraordinary rarity of coccidioidomycosis in Minnesota lies in the fact that the main reservoir for infection with C. immitis is in the distant southern agricultural valley of California, the Sacramento–San Joaquin Valley, particularly its southern reaches, including the two counties of Kern and Tulare. Approximately 90 per cent of reported cases have concerned patients observed in California, and approximately 66 per cent of cases have been reported from the central and southern sections of that state.[1] In California the disease has been reportable since 1928; yet only isolated instances have been observed in other states.

Coccidioidomycosis was discovered in Argentina; the second case was reported from California, by Rixford, and for nearly fifty years California has been a center for research concerning this disease. Tremendous strides in the understanding of the biology of the causative fungus and of the life history of the disease in man have been made by physicians working in that state. With a somewhat doubtful sense of fitness, it has even been suggested that this be known as the "California disease."

CLINICAL MANIFESTATIONS OF COCCIDIOIDAL INFECTION

Until recently the fungus C. immitis was thought to cause only one type of disease, a serious chronic granulomatous infection with clinical and pathologic features similar to those of tuberculosis. It was known to affect skin, lymph nodes, abdominal and thoracic viscera, meninges, bones and joints. In 1936 Dickson [5] and Smith [6] independently made the notable discovery that the organism may cause not only a serious chronic granulomatous process but an acute, extremely benign disease. Endemic in the Sacramento–San Joaquin Valley area for at least fifty years has been a disease well known to local members of the medical profession and to laymen as "valley fever," "desert fever," "desert rheumatism," "San Joaquin Valley fever" or "the bumps." It is a mild, usually nonfatal illness, characterized by the acute onset of malaise, general aches and pains, "toxic erythema," sore throat with fever and, occasionally, conjunctivitis, and signs of bronchopneumonia appear. Eight to fifteen days after the onset of the disease, at a time when there appears to be general improvement of the patient's condition, lesions typical of erythema nodosum appear, mainly on the shins, occasionally elsewhere on the body.[2]

5. Dickson, E. C.: "Valley Fever" of the San Joaquin Valley and Fungus Coccidioides, California & West. Med. **47**:151-155 (Sept.) 1937.

6. Smith, J., cited by Dickson.[5]

Roentgenologic examination of the thorax at the time of the appearance of erythema nodosum usually discloses the presence of opaque regions which suggest the diagnosis of tuberculosis.

The cause of this disease remained unknown until 1936, when Dickson and Smith found that the fungus C. immitis could be obtained from the sputum of a patient who had the disease. Moreover, affected persons react powerfully to the subcutaneous injection of test doses of a broth filtrate ("coccidioidin") from cultures of the organism. For these reasons it is now agreed that valley fever is caused by C. immitis.

Many patients are said never to seek medical attention when they have valley fever; others probably receive a diagnosis of "flu" or "pneumonia," especially if erythema nodosum does not appear.

MANNER OF INFECTION WITH C. IMMITIS

The organism C. immitis passes through two phases in its life cycle, one vegetative and one parasitic. The vegetative phase probably takes place in soil or on vegetation. Reproduction in this phase is accomplished by means of chlamydospores, which are minute bodies attached to aerial hyphae of the fungous growth. The parasitic phase occurs in the body of an infected host. The delicate chlamydospores of the vegetative phase may float free in the air and are capable of producing disease in the one who inhales them after an incubation period of one to three weeks. Animals may be so infected experimentally,[7] and there are on record many clearcut instances of infection resulting from inhalation of chlamydospores by human beings, especially laboratory workers who have dealt with the organism grown on artificial solid medium. Valley fever may develop in human beings who inhale the spores. It is rarely followed by coccidioidal granuloma. Only a few cases of proved "inoculation infection" have been reported.[1] One patient was believed to have acquired the infection by pricking the skin with a cactus burr, and infection also has resulted from an abrasion of the skin caused by picking walnuts, by injury with a splinter of wood and so forth. Not all patients suffering from coccidioidal granuloma have given a history of valley fever or inoculation, but this is an aspect of the problem which will require further study.

TYPES OF ARTHRITIS ASSOCIATED WITH COCCIDIOIDOMYCOSIS

Involvement of joints occurs both in the acute benign phase and in the more dangerous chronic granulomatous phase of coccidioidal infection. In cases of valley fever, or desert rheumatism, involvement of

7. Cronkite, A. E., and Lack, A. R.: Primary Pulmonary Coccidioidomycosis: Experimental Infection with Coccidioides Immitis, J. Exper. Med. **72**: 167-174 (Aug.) 1940.

joints may be distressingly painful but is nevertheless relatively insignificant because the arthritis subsides completely. Involvement of joints in the granulomatous phase of the disease is serious and may be the forerunner of disseminated infection which will lead to death.

Arthritis of Valley Fever.—Signs of acute arthritis develop in about a third of patients who have valley fever, usually appearing simultaneously with erythema nodosum.[8] Affected joints are tender to pressure, painful on motion and in some cases are slightly swollen. Effusion into these joints has not been observed, and in no known instance has suppuration taken place. Sometimes conjunctivitis also appears in this stage of valley fever, and often arthritis, conjunctivitis and erythema nodosum appear together, persist about a month and disappear at approximately the same time. Affected joints always clear without residual damage or deformity. Among older people the arthritis is said to be more prolonged than it is among children. No records of roentgenologic examination of such joints are available, to our knowledge.

Diagnosis: Valley fever should be suspected particularly among patients complaining of acute arthritis who also present evidence of acute pulmonary infection, whether or not it is accompanied by erythema nodosum. Suspicion should be heightened if the patient has been resident or visiting in southern California. Diagnosis may be established positively by the finding of the organism C. immitis in the sputum by direct examination, culture or inoculation of guinea pigs.

Prognosis: Notable differences exist between the prognosis for the common acute mild manifestation of coccidioidal infection, or valley fever, and that for the chronic granulomatous phase of the disease. Survival is the rule after the acute type of disease. In only 1 of 354 cases of valley fever known to Dickson and Gifford did the granulomatous phase develop. In this case the patient died. In none of the 432 cases collected by Smith[9] did the granulomatous phase develop. On the other hand, death has resulted in 50 per cent of cases of coccidioidal granuloma. What alteration in the mechanism of immunity or in the virulence of the infecting organism underlies this tremendously important change in prognosis is thus far not known.

Treatment: No special methods of therapy have been developed for valley fever. Affected patients are best kept at rest in bed, and measures for symptomatic relief should be employed, including the administration of salicylates, to relieve pain in joints.

8. Faber, H. K.; Smith, C. E., and Dickson, E. C.: Acute Coccidioidomycosis with Erythema Nodosum in Children, J. Pediat. **15**:163-171 (Aug.) 1939.

9. Smith, C. E.: Epidemiology of Acute Coccidioidomycosis with Erythema Nodosum ("San Joaquin" or "Valley Fever"), Am. J. Pub. Health **30**:600-611 (June) 1940.

Arthritis of the Chronic Granulomatous Phase of Coccidioidomycosis.—In this stage of the disease, lesions in bones and joints are fairly commonly encountered. Among 256 cases tabulated in the report of the California Department of Public Health in 1931,[1] involvement of joints was noted in 79, as seen in table 1. Often, several joints are involved at one time. Affected joints have in this particular phase of the disease first the appearance of acute, later of chronic, arthritis. Early, the joints are swollen and red; later, fluctuation may appear. Nodular lesions may develop in the skin overlying affected joints. Such lesions may ulcerate and discharge pus containing C. immitis. McMaster and Gilfillan [10] expressed the opinion that joints may be primarily affected by direct involvement of the synovial membrane or infection may extend to joints from adjacent foci of coccidioidal osteomyelitis. Of

TABLE 1.—*Involvement of Joints in Seventy-Nine Cases of Acute Granulomatous Coccidioidomycosis*

Joint	No. of Cases
Ankle	33
Knee	21
Foot	16
Elbow	11
Wrist	10
Shoulder	8
Finger (?)	7
Vertebrae	6
Hip	5
Sternoclavicular	1
Unspecified	5

24 cases reported by them in which involvement of bones and joints was noted, primary localization in synovial membrane was present in 4 (once in an ankle, once in a hip and twice in a knee joint). In the remaining 20 cases infection of joints had taken place by extension from adjacent areas of bone disease. Progression of the infection is not halted by articular cartilage or epiphysial bone, although intervertebral disks are somewhat more resistant than are vertebral bodies.

Roentgenographic Manifestations in Joints: These may mimic the changes seen in cases of tuberculous arthritis. Early lesions are characterized by regions of destruction in articular surfaces, often with evidence of swelling of overlying soft tissues. Cartilage may be destroyed and joint spaces narrowed. There is little tendency toward production of bone in the early lesions of the chronic stage. Later lesions in joints may cause complete disappearance of joint spaces, more

10. McMaster, P. E., and Gilfillan, C.: Coccidioidal Osteomyelitis, J. A. M. A. **112**:1233-1237 (April 1) 1939.

extensive zones of destruction in articular surfaces and, in some instances, ankylosis.[10] These lesions have been commonly mistaken for those of tuberculous arthritis. Carter [11] pointed out that arthritis both in coccidioidal granuloma and in tuberculosis is predominantly destructive, shows little tendency to heal by production of bone and frequently is accompanied by pulmonary involvement. But whereas tuberculosis appears often to attack joints directly, coccidioidal granuloma usually does so by extension from adjacent bone lesions, and the latter involvement more often affects multiple joints. Taylor [12] found the destructive process in bones, as shown by roentgenograms, to be distinguished by an intensity and rapidity of development not often noted in the presence of tuberculosis.

Diagnosis: This condition should be suspected in persons suffering from chronic progressive monoarticular or polyarticular arthritis, particularly if such persons have resided or visited in the region of the San Joaquin Valley. Suspicion should be heightened if serial roentgenograms indicate an unusually rapid progress of the destructive process in bone. As in cases of tuberculosis of bones and joints, an active primary infection may not be demonstrable. The diagnosis must rest on the finding of the organisms in sputum, tissues or pus from a sinus leading from an involved region. Occasionally, the organism has been obtained by means of blood culture.[1]

Prognosis: In most recent reports the mortality rate in the chronic granulomatous phase is stated to be at least 50 per cent. The disease kills by becoming generalized. During the terminal phase the patient may display exhaustion and high fever of a septic type, often accompanied by chills, emaciation and marked anemia.

Treatment: No therapy has proved to be of specific value for the chronic phase of this disease. Antimony and potassium tartrate, colloidal copper, vaccine, thymol and roentgen therapy have had proponents. Amputation may be a life-saving measure. Hynes [13] recently reported "startling results of sulfanilamide therapy" for 1 patient, but our own therapeutic efforts with this drug were not successful. Dr. Luther Thompson, of the Section on Bacteriology and Parasitology of the Mayo Clinic, has made some preliminary studies of the fungicidal effect of sulfanilamide in vitro, using the particular strain of C. immitis which was isolated from our patient. Thus far it would appear that sulfanilamide is not effective against the fungus. In a recent personal com-

11. Carter, R. A.: Coccidioidal Granuloma: Roentgen Diagnosis, Am. J. Roentgenol. **25**:715-738 (June) 1931.

12. Taylor, R. G.: Coccidioidal Granuloma, Am. J. Roentgenol. **10**:551-558 (July) 1923.

13. Hynes, K. E.: Coccidioidal Granuloma, Northwest Med. **38**:19-21 (Jan.) 1939.

munication, Dr. Charles E. Smith,[14] associate professor of public health and preventive medicine at the Stanford University School of Medicine, San Francisco, stated that there, too, sulfanilamide had been found to be ineffectual in treatment both of the acute and of the chronic phase of the disease in man and also in vitro and in treatment of infection produced experimentally in animals.

REPORT OF CASE

The patient, a man aged 25, came to the Mayo Clinic in October 1940, complaining of pain and swelling of both ankles of a year's duration. He had been

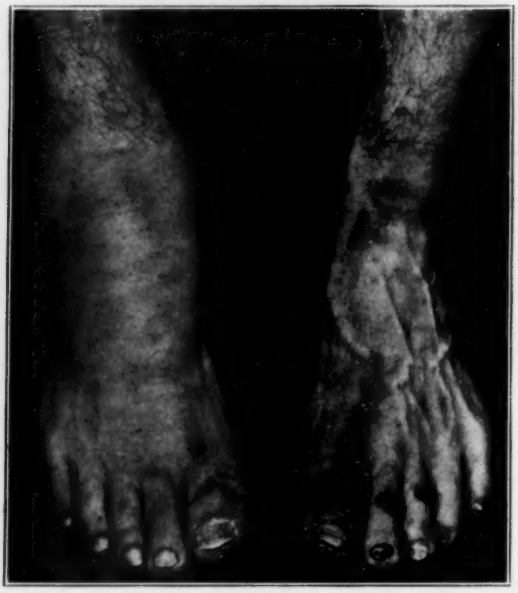

Fig. 1.—The condition of the patient's ankles on Oct. 4, 1940. Marked swelling is evident.

born in Arkansas but had lived and worked in the San Joaquin Valley, Calif., for four years previous to the onset of his illness in 1939. He had been employed as foreman of a crew of workers on oil pipe lines. The work frequently was dirty and dusty. His family history was irrelevant, and he had had no previous serious illness.

During May, June and July 1939 he had a dry cough. In July 1939 he thought he had "flu," for he "ached all over" and suffered from headache and his temperature increased to 104 F. His local physician also at first believed this illness represented influenza or grip, but after three days of fever, a generalized

14. Smith, C. E.: Personal communication to the authors.

rash appeared on the patient's face, trunk and extremities. This rash led to the diagnosis of "typhus" by his physician. The rash cleared after three or four days. Fever, during which the temperature was elevated to 102 F., continued for two weeks, and during the second week the patient had "pleurisy" on the right side, with severe pain on respiration. At this point a tuberculin test was made, to which the reaction was negative.

Low grade fever persisted. In August, four months after onset of the cough, a number of red, indurated lesions appeared on the dorsum of either hand and on the outer aspect of the left thigh. These may have represented erythema nodosum, but we could not be certain on the basis of the patient's history. These lesions persisted for two or three weeks, were slightly painful and healed without leaving any scars.

The patient was able to return to work in October 1939 but continued to have low grade fever in the afternoon. Three days after he began to work swelling appeared about the left foot and ankle, with pain on weight bearing. One week later the right foot and ankle swelled and became painful. These swellings persisted, but he continued to work. Diathermy applied to the ankles and "rheumatism" remedies taken by mouth were ineffective.

In September 1940 pain on weight bearing became intolerable and the patient quit work. His condition then remained unchanged until he came to the clinic.

Physical examination of the head, thorax and abdomen at that time failed to reveal anything abnormal. The blood pressure was 130 systolic and 90 diastolic, expressed in millimeters of mercury. Both ankles were swollen, the right more than the left (fig. 1), and on palpation the swellings gave the impression of fluctuation. Pressure over the swollen portions elicited severe tenderness. The lymph nodes overlying Scarpa's triangles were enlarged but not tender.

Laboratory studies, including urinalysis and blood counts, did not reveal any striking abnormalities. There was a slight reduction of the value for hemoglobin, to 12.7 Gm. per hundred cubic centimeters. The result of the flocculation test for syphilis was negative. Results of agglutination tests were negative for Brucella melitensis, Eberthella typhi and Proteus X_{19} (Weil-Felix agglutination reaction for typhus fever). Roentgenograms of the thorax were normal, and those of both ankles showed swellings of the soft tissue, with flecks of calcification in the swollen regions. In the left ankle joint (fig. 2) there was marked erosion of the posterosuperior border of the os calcis. Roentgenograms of the ankles in the anteroposterior position (fig. 3) showed marked clouding of the right ankle joint, with possibly some erosion of the joint surfaces.

We recognized that this patient's condition bore a resemblance to tuberculosis, but we were of the opinion that the curious features of the history and the bilateral involvement were atypical of tuberculosis and justified biopsy for final diagnosis.

On October 7 the posteromedial aspect of the right ankle was incised. Part of a sac filled with cheesy necrotic material was removed for biopsy, and culture medium was inoculated with some of the contents. The wound healed by primary intention.

The surgical specimen consisted of mottled brownish yellow tissue having the appearance of granulation tissue. Fresh frozen sections stained with polychrome methylene blue showed a granulomatous lesion with giant cells and epithelioid cells. In addition, many polymorphonuclear leukocytes and monocytes were present,

Fig. 2.—A roentgenogram of the patient's left ankle, made on Oct. 2, 1940. Periarticular swelling of the soft tissues and erosion of the posterosuperior border of the os calcis are seen. There is only slight involvement of the ankle joint. Flecks representing calcification may be noted in the soft tissues posterior to the ankle joint.

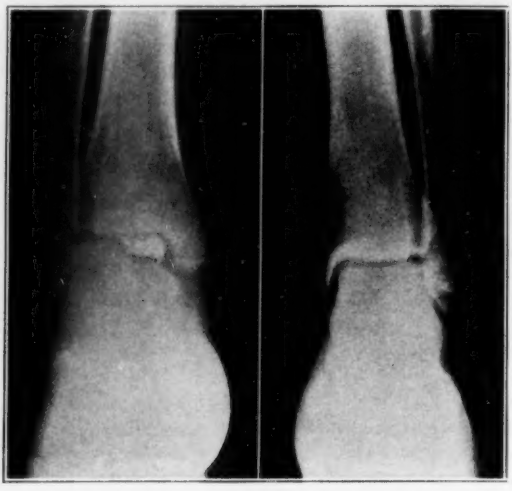

Fig. 3.—An anteroposterior roentgenogram of the ankles, made on Nov. 25, 1940, demonstrating clouding in the shadow of the right ankle joint.

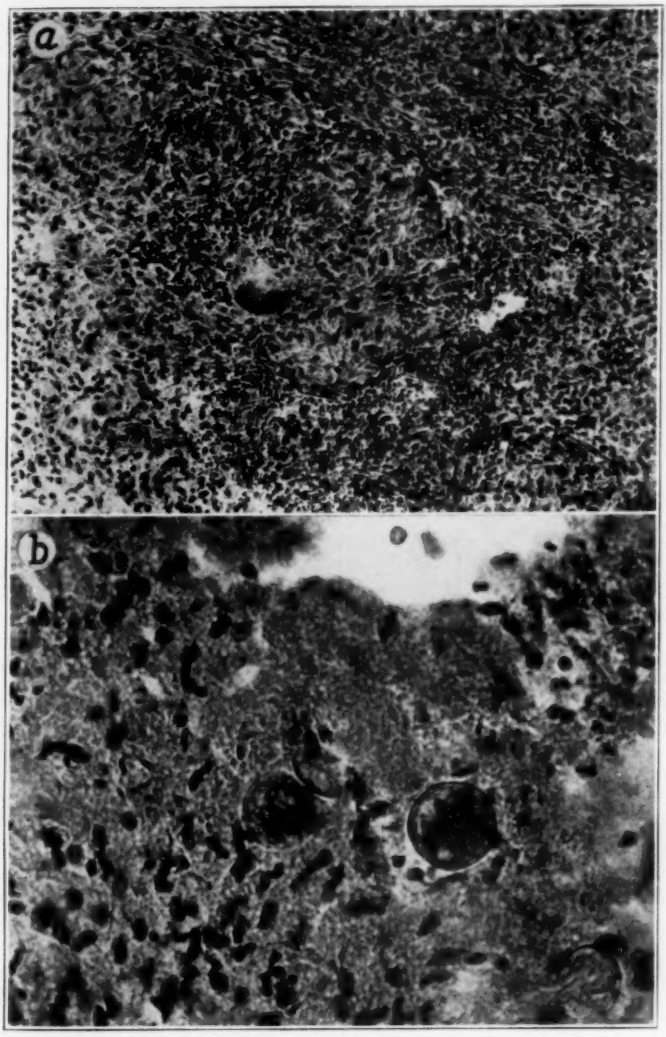

Fig. 4.—(*a*) Histologic picture similar to that found in the presence of tuberculosis, with "tubercle" formation, large giant cells and foci of acute inflammation. Hematoxylin and eosin; × 150. (*b*) Organisms of coccidioidal granuloma, with double-contoured bodies filled with spores but without budding or mycelial formation. Hematoxylin and eosin; × 450.

particularly around focal areas of necrosis, which dotted the microscopic field. Fragments of disintegrating bone in several sections confirmed the roentgenographic evidence of calcium about the joint and suggested that the process was one of destructive osteitis. Occasional "tubercle" formation was observed, which was suggestive of tuberculosis. However, search with high magnification disclosed large, double-contoured, refractile bodies containing minute, rounded, sporelike forms. Some of these double-contoured bodies were seen to be engulfed in giant cells, but others lay free in the intercellular spaces, especially in cellular zones. Budding was not observed, and no mycelial filaments were seen. A diagnosis of coccidioidal granuloma was made on the basis of this examination of fresh tissue.

Of the salient microscopic features in this case, one is shown in figure 4 *A*, in which the resemblance to tissue affected by tuberculosis is striking. Figure 4 *B*

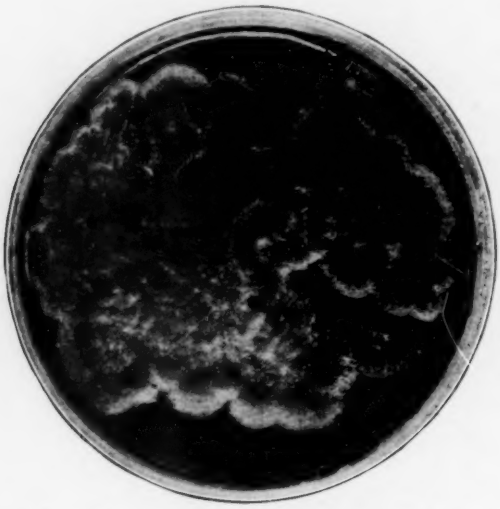

Fig. 5.—A colony of C. immitis cultured on blood agar at 22 C. in a Petri dish. The moldlike growth of this organism and the well formed aerial hyphae are evident.

illustrates the spore-filled "capsules" of the organism C. immitis. Figure 5 shows a ten day growth of the culture on blood agar at 22 C. and demonstrates the development of aerial hyphae.

Sulfanilamide was administered to the patient from October 10 through November 6, in doses of 45 to 90 grains (3 to 6 Gm.) daily. The values for concentration of sulfanilamide and hemoglobin in the blood and leukocyte counts are shown in table 2. Roentgen irradiation was administered over the ankles of the patient from October 23 to November 9, as indicated in table 3. His course in the hospital was essentially afebrile.

Roentgenograms of the ankles made on November 15 showed no significant change from those made when the patient was first admitted to our care. At the time of his dismissal his condition seemed to be essentially unaltered.

TABLE 2.—*Values for Concentration of Sulfanilamide and Hemoglobin in the Blood and Leukocyte Counts for a Patient Suffering from Coccidioidal Granuloma Treated with Sulfanilamide and Roentgen Irradiation* *

Date, 1940		Sulfanilamide in Blood, Mg. per 100 Cc.	Hemoglobin, Gm. per 100 Cc.	Leukocytes per Cu. Mm.
October	November			
2	..	....	12.7	11,300
11	..	....	14.6	6,200
14	..	....	15.9	6,700
17	..	8.2	13.2	8,400
19	..	....	15.0	9,900
21	..	10.4	12.4	8,200
23	..	....	13.5	.....
24	..	9.0	....	.....
26	..	12.0	....	8,600
28	..	11.6	....	4,700
30	..	10.4	....	7,700
	1	10.2	....	6,600
	2	13.8	....	.....
	4	11.4	9.2	6,600
	6	10.8	....	8,000
	14	....	10.0	14,500

* The schedule and record of roentgen therapy appear in table 3.

TABLE 3.—*Record of Roentgen Therapy for a Patient Suffering from Coccidioidal Granuloma*

Date, 1940		Kilovolts	Distance, Inches	Milli-amperes	Filtration (Aluminum)	Time, Minutes
October	November					
23	..	130	16	6	6 mm.	5
28	..	130	16	6	6 mm.	5
	1	130	16	6	6 mm.	5
	5	130	16	6	6 mm.	5
	9	130	16	6	6 mm.	5

TABLE 4.—*Differential Diagnosis of Coccidioidal Granuloma, Blastomycosis and Torulosis* *

		Histologic Considerations				
Organism	Disease Caused	Histologic Reaction	Cellular Products	Budding	Spores	Distribution of Lesions
C. immitis	Coccidioidal granuloma	Acute, with polymorphonuclear leukocytes	None	Never	Always	Skin; generalized (especially lungs)
Blastomyces dermatitidis †	Blastomycosis	Acute, with polymorphonuclear leukocytes	None	Always	Never	Skin; generalized (especially lungs)
Debaromyces neoformans	Torulosis	Mild; chronic	Mucoid material	Sometimes	Never	Usually brain, meninges

		Laboratory Considerations			
		Organisms in Culture			
Organism	Disease Caused	Mycelium	Ascospores	Colonies	Pathogenicity (For Animals)
B. dermatitidis	Blastomycosis	Always	Never (?)	Dry, "fuzzy"	Slight or absent
C. immitis	Coccidioidal granuloma	Always	Never	Dry, "fuzzy"	Marked for all laboratory animals
D. neoformans	Torulosis	Never	Recently demonstrated	Moist (mucoid)	Marked for rats and mice, slight for guinea pigs (principally lesions in the brain)

* Adapted, with minor changes, from W. McK. Craig, M. B. Dockerty and S. W. Harrington: Intravertebral and Intrathoracic Blastomycoma Simulating Dumb-Bell Tumor, South. Surgeon 9: 750-766 (Oct.) 1940.

† The fungus Zymonema dermatitidis has been named by some as the etiologic agent in blastomycosis. However, because absolute proof is lacking, Henrici and others expressed themselves to be in favor of retaining this older term, manifestly inaccurate but justified on the basis of usage.

COMMENT

Blastomycosis, coccidioidomycosis and torulosis are at times difficult to differentiate. Table 4 (modified from Benham) has been included here for those who, like us, encounter these conditions only occasionally. It presents briefly the chief laboratory and histologic points in the differential diagnosis of coccidioidal granuloma, blastomycosis and torulosis.

SUMMARY

The phenomena of coccidioidomycosis are briefly reviewed, and a case is reported of coccidioidomycosis of the ankle joints, in which chemotherapy with sulfanilamide alone and in combination with roentgen irradiation proved to be ineffective. Failure of sulfanilamide to act as a fungicide for C. immitis in vitro has been recorded.

EDEMA WITH UNEXPLAINED HYPOPROTEINEMIA

A SYNDROME OF DEFECTIVE FORMATION OF SERUM PROTEINS IN THE ABSENCE OF "LOSS AND LACK" OF PROTEIN AND DEMONSTRABLE HEPATIC DISEASE

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Until lately the state of hypoproteinemia has been explained as the consequence either of loss of body protein, such as occurs in nephritis, or of the lack of dietary protein. Recently Bloomfield,[1] Melnick and Cowgill [2] and others have shown the inadequacy of this "loss and lack" theory and have pointed to defective formation of serum proteins as a factor in the reduction of serum protein concentration.

Some of the evidence favoring the hepatic origin [3] of the plasma proteins derives from reported cases [4] of hepatic disease with hypoproteinemia apparently due to defective protein formation (without loss of ascitic fluid). In cases of nephritis such impairment of protein formation is more difficult to demonstrate, even though the serum protein concentration may decline in some patients who lose only a few grams of protein in the urine, while in other patients (and in rats after subtotal nephrectomy [5]) relatively huge amounts of protein may be lost without material alteration of the amount of protein in the serum.

This great variation in the tolerance of different persons to protein loss suggests the possible existence of a state with defective formation of serum proteins in which edema might occur with otherwise unexplained

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hypoproteinemia, without loss or lack of protein and without hepatic or renal disorder. Such a syndrome seems actually to occur; 4 cases have been reported, and some detailed observations on a fifth case are presented in this paper.

REPORT OF A CASE

E. M. B., an American housewife aged 24, entered Lane Hospital June 10, 1940 for study of swelling of her legs.

History.—Her father had died at the age of 47 of coronary arteriosclerosis; her mother, aged 45, was well. Six brothers and sisters were alive and well.

The patient had always lived in Oregon or California. She had had measles, chickenpox and diphtheria in early childhood. When she was 6 years old, a fall had resulted in partial paralysis of the "entire left side," with full recovery in six months; in 1931, when the patient was 15 years old, an adenotonsillectomy had been performed. She had never been pregnant and had been entirely healthy up to the time of the illness reported here, which began eight years ago, in 1933.

In March 1934 she visited another hospital because of swelling and redness of the left leg of two weeks' duration. The record made at that time notes that both legs had been swollen for a year. There were no other symptoms. Examination then revealed soft pitting edema of the left leg to the knee and less edema of the right leg halfway to the knee. There was a tender red area just above the left ankle, but veins, lymphatics and lymph nodes were not tender. Her oral temperature on admission was 100 F.; it dropped rapidly to 98 F. and stayed normal during eighteen days of hospitalization. The white blood cell count was 7,700 per cubic millimeter, and a roentgenogram of the left leg was normal. Treatment consisted of rest in bed and application of hot compresses; the edema disappeared.

Soon, however, the swelling returned in both legs, without constitutional symptoms; at first it was present only toward night, but later the legs were swollen all day long, and the patient again noted that pressure left a deep pit. At that time the edema was cyclic, with no apparent correlation with menses or anything the patient did (except that it was perhaps worse when she was mentally upset and better when calm); the edema would be present one or two months and absent for the same length of time. Later it was present always but varied in intensity; sometimes even the thighs and the lower part of the back were swollen, sometimes only the ankles.

Early in 1939 she sought relief at another hospital. Nothing was found but pitting edema. The blood count and the urine were normal. More pertinent were a normal reaction to the rose bengal test and a total plasma protein concentration of 3.95 Gm. per hundred cubic centimeters, with 2.68 Gm. of albumin and 1.27 Gm. of globulin. Digitalis and a low salt diet were prescribed. However, the edema persisted; in April 1940 she was again hospitalized, but nothing was noted save edema, a normal Takata-Ara reaction and a total serum protein concentration of 3.80 Gm. per hundred cubic centimeters. She finally entered Lane Hospital for study on June 10, 1940.

Dietetic History.—During her high school years (1930-1934) the patient ate for breakfast a large dish of cereal, 2 slices of buttered toast, fruit and a pint (473 cc.) of milk, with an egg every other day. At lunch she had vegetables, potato, fruit and bread or fruit and sandwiches. Dinner consisted of salad, potato, vegetables, bread and dessert; never liking meat well, she ate it (usually lamb or lamb chops) only twice a week. Between meals she ate apples, candy,

crackers and cheese in moderation. From 1935 to 1939 she quit taking milk at breakfast (because of indigestion) but had ice cream or a milk shake at night; otherwise the diet was about the same as before. So from 1930 to 1939 the diet was adequate; its protein content ranged from perhaps 60 to 100 Gm. daily, averaging about 65 to 70 Gm.

A few months after discovery of the low plasma protein concentration on Feb. 6, 1939, a physician prescribed a high protein diet. The patient added to the aforementioned diet a pint and a half (700 cc.) of milk daily, 6 eggs a week, bacon (3 strips) twice a week, a half pound (227 Gm.) of cheese weekly, meat sandwiches at noon every other day and 2 lamb chops (or a small steak, 2 slices of liver or a piece of ham) each night. The diet has raised the intake of protein to 100 to 120 Gm. a day for the past year.

Physical Examination.—The patient did not appear ill; she was well developed and a bit obese, 170 cm. in height and 82.0 Kg. in weight (later 75.7 Kg. in remission). The head and neck were normal; there was no venous distention, and the eyelids were not swollen. The lungs were clear. The heart was not enlarged, and its sounds were normal. The cardiac rate was not rapid (56 per minute under basal conditions), and the blood pressure was 125 systolic and 75 diastolic, measured in millimeters of mercury. There was no fever. The abdomen was normal; neither liver nor spleen was palpable. There was no jaundice, and no spider angiomas were present. Pelvic, rectal and neurologic examinations yielded nothing abnormal. There was marked soft pitting edema of both lower extremities (a little more on the right side) and of the back as high as the level of the third lumbar vertebra. The skin was dusky red over both tibias (each area measuring 10 by 25 cm.), and these regions were tender, but there were no tender or palpable cords over the courses of the veins or the lymphatics of the leg. Lymph nodes were not enlarged.

Laboratory Studies.—The blood count showed 5,450,000 erythrocytes and 8,000 leukocytes per cubic millimeter. There was 15.8 Gm. of hemoglobin per hundred cubic centimeters (92 per cent Sahli). The erythrocytes were a little thicker (2.4 microns) than normal and averaged only 6.5 microns in diameter, with none over 7.5 microns; the mean corpuscular volume (80.1 cubic microns) and the mean corpuscular hemoglobin content (28.9 micromicrograms) were at the lower limit of normal, while the mean corpuscular hemoglobin concentration was normal (36.1 per cent). There were 167,400 reticulocytes (3.1 per cent of the erythrocytes) and 405,000 platelets per cubic millimeter. Fragility to a hypotonic solution of sodium chloride was normal, hemolysis starting at 0.46 per cent and ending at 0.24 per cent. The differential white count revealed 7 per cent eosinophils (560 per cubic millimeter), 1 per cent basophils, 8 per cent monocytes, 16 per cent lymphocytes and 68 per cent polymorphonuclear neutrophils (16 per cent banded and 52 per cent segmented). The clotting time of the whole blood was four and a half minutes and that of plasma five minutes; the clot retracted normally. The sedimentation rate was only 3 mm. in an hour.

The results of routine urinalysis were negative, and an Addis sediment count failed to reveal any casts or red blood cells and disclosed only 2,000,000 white blood and epithelial cells in a twenty-four hour specimen; there was only the normal immeasurably small amount of protein. The amount of urobilinogen in the urine was normal.

The stool was soft and brown, and did not contain any occult blood, parasites, fat, starch granules or muscle fibers; there were rare vegetable cells. Nitrogen in the stool was less than 1 Gm. per day.

The basal metabolic rate was —2.3 per cent. An electrocardiogram showed only left axis deviation. The highest ten minute volume of gastric juice secreted after the administration of histamine was 37 cc., with 22 degrees free hydrochloric acid and 31 degrees total acid. Roentgenograms of the chest and of the kidneys after intravenous injection of diodrast were normal. The Wassermann reaction of the blood was negative, as was the cutaneous reaction to tuberculin in a dilution of 1:10,000.

There was no retention of bromsulphalein (5 mg. per kilogram of body weight) in the blood thirty minutes after injection. Two grams of sodium benzoate was injected intravenously; from the urine voided during the succeeding two hours 1.12 Gm. of hippuric acid (as benzoic acid) was recovered (a normal rate of excretion). The icterus index was 1; the direct van den Bergh reaction was negative, and the concentration of bilirubin was only 0.03 mg. per hundred cubic centimeters.

The concentrations of various substances in the blood, expressed in milligrams per hundred cubic centimeters, were as follows: dextrose, 84 (three hours after

TABLE 1.—*Nitrogen Balance of a Patient with Edema and Unexplained Hypoproteinemia*

Date, June 1940	Daily Intake of Nitrogen, Gm.	Daily Output of Nitrogen, Gm.			Balance,* Gm.
		Urine		Stool, Total Nitrogen	
		Urea Nitrogen	Total Nitrogen		
18	24.1	14.5	....	...	+7.6
19	21.4	12.3	....	...	+7.1
20	22.7	14.0	15.4	0.4	+6.7
21	17.8	14.0	14.8	1.7	+1.8
22	21.1	13.2	....	0.8	+5.9
23	16.6	12.6	....	...	+2.0
24	16.5	8.9	....	...	+5.6
Mean	20.0	12.8	....	0.97	+5.2

* The daily loss of 1 Gm. of nitrogen in the stools and 1 Gm. of nonurea nitrogen in the urine is assumed.

breakfast); calcium, 7.1 (serum); inorganic phosphorus, 3.3 (serum); phosphatase (and amylase), normal; cholesterol, 145; uric acid, 1.3 (serum) and 2 (whole blood); amino acid nitrogen 4.0 (serum) and 6.2 (whole blood), and urea, 25.5. The blood volume was 6,260 cc. (82 cc. per kilogram of body weight, 3.3 liters per square meter of body surface), and the plasma volume 3,380 cc. Of injected congo red, 80 per cent remained in the serum at the end of one hour.

The total serum protein was determined thirteen times in nine months and was found to vary from 3.00 to 4.68 Gm. per hundred cubic centimeters (average 3.86 Gm.). Fractionation of the serum with salts once showed the concentration of albumin and globulins to be 2.3 and 1.3 Gm. per hundred cubic centimeters, respectively (total 3.6 Gm.). On another occasion, with a total serum protein concentration of 4.49 Gm. per hundred cubic centimeters, electrophoretic analysis by Dr. Eloise Jameson yielded the following results in terms of grams of protein per hundred cubic centimeters of serum; albumin, 2.83; alpha globulin, 0.27; beta globulin, 0.70; gamma globulin, 0.69, and total globulins, 1.66. On the two occasions the albumin-globulin ratio was 1.70 and 1.77. The concentration of fibrinogen was 0.29 and 0.30 Gm. per hundred cubic centimeters of plasma, respectively.

Course of Illness.—As later events indicated, the patient entered the hospital at the start of a spontaneous partial remission, with a serum protein concentration of 4.3 to 4.6 Gm. per hundred cubic centimeters. The edema promptly diminished from the legs and the lower part of her back as her weight fell from 82.0 to 75.7 Kg.

Her daily diet contained about 150 Gm. of protein and 2,340 calories; after a week the observations on nitrogen balance were made as recorded in table 1. While the data are incomplete, they show a positive nitrogen balance, in spite of the appearance of herpes zoster (afebrile) at the left sixth thoracic segment on June 17. She left the hospital June 25, weighing 75.9 Kg.

When examined in the outpatient department two weeks later she again weighed 81.5 Kg. and was grossly edematous, with a serum protein concentration of 3.42 Gm. per hundred cubic centimeters, in spite of the high protein diet and large doses of thiamine hydrochloride.

The degree of edema, weight, total serum protein concentration and protein intake for E.M.B. Note three spontaneous partial remissions and the absence of any correlation between protein intake and the serum protein concentrations or remissions.

At this time she was plagued by family and financial troubles, went on relief and could obtain an average of only 35 Gm. of protein in her daily diet (bacon, 1 egg, toast, soup, potatoes, lettuce, carrots and buttered bread, with milk twice a week). Yet she returned at the end of July almost free of edema, weighing 77.6 Kg. and with a serum protein concentration of 4.68 Gm. per hundred cubic centimeters (figure).

In October she took amino acid powder by mouth, with no effect. A third spontaneous partial remission occurred in December but was not observed. For eighteen days in January and February she took her meals under observation in the hospital, eating food high in vitamins and averaging 100 Gm. of protein and 2,000 calories daily; her weight increased from 80.6 to 83.4 Kg., without obvious

change in the amount of edema, while the serum protein concentration fell slightly (3.9 to 3.6 Gm. per hundred cubic centimeters).

Throughout these nine months she underwent observation rather grudgingly and was unwilling to permit such therapeutic attempts as a low salt diet, administration of diuretics or transfusions; therefore the data just reported represent practically the spontaneous course of this disorder.

COMMENT

The first clinical problem was to determine the cause of the edema; it was undoubtedly hypoproteinemia. Then an unsuccessful search was instituted for known causes of hypoproteinemia (table 2). There was

TABLE 2.—*Physiologic Causes of Hypoproteinemia*

A. Loss and destruction of body protein	
I. Urine	**(Bright's disease)**
II. Ascitic fluid	**(cirrhosis with paracenteses)**
III. Tissue	**(cachexia)**
IV. Fetus	**(pregnancy)**
B. Retarded formation of serum protein	
I. Lack of dietary protein	
(a) Absolute total dietary insufficiency	
(1) Starvation	
(2) Pyloric obstruction	
(3) Diarrhea	
(b) Relative total dietary insufficiency	
(1) Pregnancy	
(2) Hyperthyroidism	
(3) Diabetes mellitus	
(c) Dietary protein deficiency	
(1) Low protein diet	
(2) Pancreatic disease	
II. Altered states of the body	
(a) Normal	
(1) The newborn	
(b) Abnormal	
(1) Hepatic disease	
(2) Bright's disease	
(3) Beriberi	
III. Unexplained	

no loss of body protein in the urine or in ascitic fluid; no destruction (see urinary nitrogen loss, table 1), as in cachexia, and no sidetracking, as in new tissue growth. There was neither absolute lack of food, as in starvation, vomiting or diarrhea, nor relative lack as in pregnancy, hyperthyroidism or diabetes mellitus. There was no specific dietary deficiency of protein (except, fortunately, while the patient was under observation; even then it did not prevent two remissions) and no loss of nitrogen in the stool through any defect of protein absorption, as in pancreatic disease.

Beriberi was excluded by the absence of neuritis and cardiac disturbances and by the failure of thiamine to induce a remission. Bright's disease was not present. Hepatic disease was, of course, impossible to exclude, but its presence was improbable for the following reasons: In the history there were no etiologic factors, such as alcoholism; the patient

had never been jaundiced, and after eight years of illness any disease of the liver should have been fairly obvious if present. Furthermore, physical examination failed to reveal jaundice, spider angiomas or ascites; neither the liver nor the spleen was palpable. Finally, laboratory studies showed a low icterus index and concentration of bilirubin in the blood, a normal amount of urobilinogen in the urine, normal results of the bromsulphalein and hippuric acid tests, normal plasma coagulation time and small erythrocytes.

The hypoproteinemia was not due to mere dilution by an increased blood plasma volume, for measurement revealed a normal volume (incidentally, the congo red method used indicated the absence of amyloidosis). It was not familial, or at least no other members of the family were edematous. A final diagnosis of hypoproteinemia due to an unexplained retarded formation of serum protein was made, and interest then turned to a study of the blood proteins themselves.

Those plasma proteins concerned with blood coagulation (and formed in the liver—fibrinogen and prothrombin) were normal. Hemoglobin was also normal in concentration. Albumin and the serum globulins were reduced proportionately, so that the albumin-globulin ratio was normal. By comparing the protein fractions obtained by electrophoresis with the most recently published normal standards,[6] one may calculate the total plasma protein of the patient at 73 per cent of normal; albumin, at 70 per cent; fibrinogen, at 78 per cent and globulins, alpha, beta and gamma, at 59, 82 and 92 per cent, respectively. (These changes are not similar to those found [6] in cases of "nephrosis," cirrhosis, heart failure, etc.) While the usual level of total serum protein was about 3.9 Gm. per hundred cubic centimeters, it once dropped to 3.0 Gm. and twice was observed to rise to 4.5 and 4.7 Gm., respectively. This behavior could not be correlated with any other changes.

In a search for other abnormalities the formed elements of the blood were of interest. Certain rather subtle changes, easily overlooked in casual examination, were found: eosinophilia, reticulocytosis and slight increase in thickness but decrease in diameter of the erythrocytes, with volume at the lower limits of normal. No disease of allergic origin or parasite was found (and no liver extract given) which might explain the eosinophilia. The latter has been described,[7] however, in association with chronic nephritis (though not necessarily with edema), and attempts have been made [8] to link eosinophils with protein metabolism.

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I know of an unreported case of starvation edema in which during recovery the eosinophils inexplicably rose to 25 per cent of 12,700 leukocytes.[9] As to the reticulocytosis and the erythrocyte shape, a fragility test yielded a normal result. The amount of urobilinogen excreted in the urine was normal, and the blood level of bilirubin was not elevated.

As a matter of fact, the icterus index was only 1, and the level of bilirubin in the blood was as low as 0.03 mg. per hundred cubic centimeters. Uric acid in the serum was also at the lower limits of normal (1.3 mg. per hundred cubic centimeters). With clinical attention centered on jaundice and gout, not much seems to be known concerning decreased concentrations of bilirubin and uric acid. Both have been said to be adsorbed by serum albumin [10] and so might be expected to be low in the hypoproteinemic state, just as serum calcium is low. But the experiments with albumin adsorption of bilirubin were concerned with high concentrations of bilirubin, and it has since been observed that the amount of bilirubin in the blood need not be decreased in all cases of hypoproteinemia.

A decrease in blood amino acid nitrogen, such as has been noted at times in cases of "nephrosis," [11] was not found. Cholesterol was somewhat lower than usual in the blood (145 mg. per hundred cubic centimeters), another bit of evidence against the theory that it rises in patients with nephritis and associated edema to increase the plasma colloidal osmotic pressure.

Finally, table 3 presents a comparison of the findings in this case with those in 4 cases of a similar condition previously reported.[12] The patients were all young, and all but 1 were women. The duration of illness is as long as eight years (possibly twelve years in Johansen's case, in the difficultly decipherable report of which nothing is found about the necropsy prematurely reviewed [3]). One patient was "infantile," 1 had a uterine fibroid and 1 had been edematous in a "normal" pregnancy eight years before study but not edematous in a pregnancy three years later.

The serum protein concentration was determined repeatedly for 4 patients: The averages for each were similar, 3.8, 3.9, 4.1 and 4.3 Gm.

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per hundred cubic centimeters. The similarity is even more striking in the case of serum albumin, values for this averaging 2.5, 2.5, 2.6 and 2.6 Gm. per hundred cubic centimeters. The concentrations of the serum globulins were 1.3, 1.5, 1.6 and 1.9 Gm. per hundred cubic centimeters. The albumin-globulin ratios were all normal, 1.5, 1.6, 1.7, 1.8 and 2.1. The concentrations of fibrinogen were normal or slightly elevated.

While the average concentrations of total protein were similar when values for different patients were compared, each person presented striking spontaneous fluctuations (0.9 to 3.1 Gm. per hundred cubic centimeters) of 20 to 80 per cent of his own mean value. These were mirrored in the 6.4 and 7.7 kilogram variations in weight of the 2 subjects who received no diuretics. These changes in the serum protein levels were not related to the dietary protein; intakes of 1.5 to over 2.5 Gm. of protein per kilogram of body weight per day did not increase the concentrations of serum protein, even though the nitrogen balance was shown to be positive for 3 patients.

None lost protein in the urine or by other routes, and at least 2 did not lose nitrogen excessively in the stools.

Each patient had at least one test of hepatic function with normal results; 3 were shown not to be icteric, and in the present case a battery of tests and circumstances rather conclusively excluded hepatic disease. In no case could it be shown that the state of hypoproteinemia had damaged the liver [13] (the patient studied by Myers and Taylor [4a] had a history of alcoholism).

Red blood cell counts and hemoglobin concentrations were normal for all 5 patients, and for 2 the white count given was normal (but see the report for further studies of the blood cells in the present case). The Wassermann reaction of the blood was negative in all cases, the tuberculin reaction in 3 and the basal metabolic rate in 4. There was gastric anacidity in 1 case (normal secretion in 3).

As expected, the oncotic pressure of the serum was reduced in the 1 patient for whom it was measured, and in another the protein concentration in the edema fluid was only 0.14 Gm. per hundred cubic centimeters.

The blood volume was normal in both cases in which it was studied. The concentrations of nonprotein nitrogen in the blood were all normal; those of cholesterol were all normal or low, and those of serum calcium were at times surprisingly normal (at other times low, as expected).

Of further interest may be the slow sedimentation rate (1 mm. per hour) and the low concentration of bilirubin (under 1.0 mg. per hundred

13. Elman, R., and Heifetz, C. J.: Experimental Hypoalbuminemia: Its Effect on the Morphology, Function, and Protein and Water Content of the Liver, J. Exper. Med. **73**:417-430 (March) 1941.

TABLE 3.—*Comparison of Data in Five Cases of Unexplained Hypoproteinemia*

	Author				
	Rytand	Cope and Goadly [12a]	Johansen [12b]	Binger and Keith [12c] (case 2)	Binger and Keith [12c] (case 3)
Age of patient, years	24	20	25	35	49
Sex	Female	Male	Female	Female	Female
Duration of edema, years	8	1½	?12	3	¼
Weight, Kg.	75.7 to 83.4	63.6 to 70.0	....	66.9 to 74.0	50
Total serum protein: Mean, Gm. per 100 cc.	3.86	4.32	3.26	3.91	4.1
Range, Gm. per 100 cc.	3.00 to 4.68	3.70 to 4.64		2.7 to 5.8	3.6 to 4.5
Serum albumin: Mean, Gm. per 100 cc.	2.56	2.63	2.10	2.63	2.5
Range, Gm. per 100 cc.	2.30 to 2.83	1.94 to 3.13		1.4 to 4.0	2.4 to 2.6
Serum globulins: Mean, Gm. per 100 cc.	1.48	1.69	1.16	1.28	1.65
Range, Gm. per 100 cc.	1.30 to 1.66	1.51 to 1.89		1.0 to 1.9	1.6 to 1.7
Albumin-globulin ratio: Mean	1.73	1.58	1.81	2.08	1.5
Range	1.70 to 1.77	1.09 to 2.07		1.0 to 2.9	1.5 to 1.5
Fibrinogen: Mean, Gm. per 100 cc.	0.29	0.64	0.37	0.56	.....
Range, Gm. per 100 cc.	0.29 to 0.30	0.45 to 0.80		0.43 to 0.68	
Loss of protein	None	None	None	None	None
Stool nitrogen, Gm. per day	0.97	1.7	.....	.....	.....
High protein diet without benefit, Gm. per Kg. per day	1.5	2.6		1.6	2.5
Nitrogen balance	Positive	Positive	"Normal"	.....	.....
Tests of hepatic function					
Levulose tolerance	.....	Normal	.....	.....	.....
Galactose tolerance	.....	.....	Normal	.....	.....
Congo red (amyloid)	Normal	.....	.....	.....	.....
Takata-Ara	Normal	.....	.....	.....	.....
Rose bengal excretion	Normal	.....	.....	.....	.....
Bromsulphalein excretion	Normal	.....	.....	Normal	Normal
Hippuric acid excretion	Normal	.....	.....	.....	.....
Icterus index, units	1.0	.....	.....	.....	.....
Serum bilirubin, mg. per 100 cc.	0.03	.....	.....	1.0	1.0
Urinary urobilinogen	Normal	.....	.....	.....	.....
Plasma clotting time, minutes	5 (normal)	.....	.....	.....	.....
Blood clotting time, minutes	4½	.....	.....	.....	.....
Hemoglobin, Gm. per 100 cc.; per cent Sahli	15.78; 92	18.4; 107	15.9; 93	13.8; 81	14.9; 87

Erythrocytes					
Number per cubic millimeter	5,450,000	5,600,000	4,800,000	4,630,000	4,840,000
Mean corpuscular volume, cubic microns	80.1	.....	.....	.....	.....
Thickness, microns	2.4	.....	.....	.....	.....
Diameter, microns	6.5	.....	.....	.....	.....
Fragility	Normal	.....	.....	.....	.....
Reticulocytes, per cent, number	3.1; 167,400	.....	.....	.....	.....
Sedimentation rate, mm. per hour	3	.....	.....	.....	.....
Platelets, number per cubic millimeter	405,000	.....	.....	.....	.....
Leukocytes, number per cubic millimeter	8,000	10,500	.....	.....	.....
Leukocytes, differential count	7% eosinophils	"Normal"	.....	.....	.....
Whole blood, cc. per Kg	82	.....	.....	73	.....
Plasma, cc. per Kg	44	.....	.....	43	.....
Concentrations, mg. per 100 cc.					
Calcium in serum	7.1	8.8 to 10.1	10.2	6.5 to 10.0	8.3
Dextrose in blood	84.3	.....	.....	"Normal"	.....
Cholesterol in blood	145.6	.....	116	133 to 231	172
Urea nitrogen in blood	11.9	.....	8.9	11.2 to 18.7	8.4
Nonprotein nitrogen in blood	.....	23 to 44	.....	29	.....
Amino acid nitrogen in serum	4.9	.....	.....	.....	.....
Amino acid nitrogen in blood	6.2	.....	.....	.....	.....
Uric acid in serum	1.3	.....	.....	.....	.....
Uric acid in blood	1.9	.....	.....	.....	.....
Chlorides as sodium chloride in plasma	.....	.....	.....	606	609
Gastric juice: Free hydrochloric acid	22°	82°	"Hypoacidity"	Anacidity	.....
Enzymes and endocrine substances	Serum phosphatase and blood amylase normal	.....	Urinary diastase, estrogen and gonadatropin normal	.....	.....
Basal metabolic rate, per cent	−2	.....	−3	+2	+9
Serum oncotic pressure, mm. of water	.....	.....	205 to 225	.....	.....
Edema fluid protein, Gm. per 100 cc.	.....	.....	.....	0.14	.....
Biopsy of bone marrow	.....	.....	Normal	.....	.....
Specific dynamic action of protein	.....	Normal	.....	.....	.....
Blood transfusion	.....	.....	Temporary relief	.....	.....

cubic centimeters; icterus index, 2.0) in the blood in the case reported by Myers and Taylor,[4a] which were similar to the findings in my case.

Treatment (other than with diuretics[12c]) was unsatisfactory. Amino acid feeding was not beneficial in 2 cases, nor were high protein diets in any of 4. Only 1 patient was given blood transfusions, with temporary relief (note a remission for one month after transfusion in a child with hepatic disease[4b]).

As to any bearing on the site of production of the serum proteins, the changes observed in all these cases, especially those (abnormal size of erythrocytes, reticulocytosis, eosinophilia and perhaps the low concentrations of uric acid and bilirubin in the serum) in the case reported here, suggest not the liver[3] but the bone marrow[14] or the reticuloendothelial system. A biopsy of the bone marrow yielded "normal" results in 1 case.

SUMMARY

The case is reported of a young woman who was edematous for eight years because of hypoproteinemia, for which none of the usual causes appeared to be present. Four previously reported cases of a similar condition are summarized and compared.

CONCLUSIONS

There is a syndrome in which the formation of serum proteins is inexplicably defective. Such a defect also plays a part in those patients with chronic nephritis in whom hypoproteinemia occurs and perhaps in patients with other disorders in which the maintenance of a normal concentration of serum proteins imposes unusual strain on the mechanism. The syndrome here described may be but an exaggerated expression of the varying abilities of different persons to form serum protein; while ordinarily loss of protein or nitrogen is required to unmask such differences, here the defect appears spontaneously.

Although the liver undoubtedly forms some of the plasma proteins, the evidence discussed here suggests bone marrow (or the reticuloendothelial system) as another site.

14. Sabin, F. R.: Cellular Reactions to a Dye-Protein with a Concept of the Mechanism of Antibody Formation, J. Exper. Med. **70**:67-82 (July) 1939.

DESTRUCTIVE OSSEOUS LESIONS IN EARLY SYPHILIS

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Early in the course of acquired syphilitic infection, spirochetes are widely disseminated throughout the body tissues, including those of the bony skeleton.[1] Yet despite the fact that bone, together with its periosteum and marrow cavity, is known to harbor virulent organisms, the development of objective skeletal abnormalities during the early stages of the disease is comparatively rare. When the skeletal structures do become involved during early syphilis, the involvement is usually proliferative periostitis. More rarely destructive osteitis and osteomyelitis occur. It is with the latter lesions that this study is concerned.

In a series of approximately 10,000 cases of early syphilis observed in the Syphilis Division of the Medical Clinic and the wards of the Johns Hopkins Hospital over a twenty-two year period (1919-1940), 15 instances of destructive bone lesions (osteitis, osteomyelitis, osteoperiostitis) have been recognized. In view of the rarity of these conditions and the relative scarcity of existing information on the subject, we report these cases and summarize the available literature.

Because of its painful nature, skeletal syphilis was one of the first manifestations of the disease to be recognized, and lucid descriptions of characteristic osteocopic pains and bony swellings appear in the writings of many of the earliest syphilologists. Nevertheless, lacking the diagnostic facilities afforded by the roentgen ray, these early clinicians were unable accurately to differentiate proliferative periosteal lesions from those in which actual bone destruction had occurred. Swediaur,[2] for example, after describing "periostitis, exostoses and a corruption of the substance of the bone known as caries," asserted that

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1. Neisser, A.: Beiträge zur Pathologie und Therapie der Syphilis, Berlin, Julius Springer, 1911, p. 101.

2. Swediaur, F. X.: Traité complet sur les symptômes, les effets, la nature et le traitement des maladies syphilitiques, ed. 4, Paris, 1801, pp. 179-188.

TABLE 1.—*Summary of Previously Reported Cases*

Author	Date	Patient: Race and Sex	Patient: Age, Yr.	Evidence of Early Syphilis: Primary	Evidence of Early Syphilis: Secondary	Evidence of Early Syphilis: Dark Field Examination	Evidence of Early Syphilis: Serologic Reaction	Skeletal Lesion: Bone Involved	Skeletal Lesion: Type of Involvement	Associated Lesions and Conditions	Relation to Primary or Secondary Syphilis	Effect of Specific Treatment	Comment
Nitchew [1] (*a*)	1932	White ♂	22	+	+	—	+	Skull	Osteoperiostitis	Cutaneous and serologic relapse; anorexia and diarrhea	3 wk. after secondary	Symptomatic relief with a bismuth compound	Moderate constitutional reaction; symptoms followed treatment with neoarsphenamine, during serologic and cutaneous relapse
(*b*)	1932	White ♀	23	—	+	..	+	Tibia	Osteoperiostitis	None	135 days after secondary	Symptomatic relief after 3 injections of a bismuth compound	Symptoms followed treatment with neoarsphenamine, after serologic reversal
(*c*)	1932	White ♂	26	+	—	+	—	Tibia	Osteoperiostitis	None	105 days after primary	Symptomatic relief after 5 injections of a bismuth compound	Contact case *b*; symptoms followed treatment with neoarsphenamine, started in seronegative primary stage
Gougerot, Mathieu and Jais [8]	1932	White ♂	55	—	+	..	+	Clavicle	Osteitis	None	40 days after secondary	Symptomatic relief and healing by roentgen examination after treatment with a bismuth compound	Pathologic fracture, which healed well after antisyphilitic treatment
Bloom [9]	1934	Negro ♀	20	—	+	..	+	Clavicle	Osteitis	Facial palsy	About 1 mo. after secondary	Symptomatic relief; arrest after 4 mo. treatment apparent in roentgenogram	Symptoms followed 2 injections of a bismuth compound and 1 of neoarsphenamine
Tauber and Goldman [10]	1935	Negro ♂	38	+	—	+	+	Skull; tibia; clavicle; scapula	Osteitis	Macrocytic anemia; weight loss; reaction of spinal fluid positive for syphilis	Indefinite	Symptomatic improvement; improvement apparent in roentgenogram after 2 mo.	Lesions like those of multiple myeloma; spinal fluid positive; biopsy
Mandelbaum and Saperstein [21]	1936	White ♀	29	—	—	..	+	Skull; sternum	Osteoperiostitis	None	8 to 12 wk. after blood transfusion	Serologic reversal in 4½ mo.; healing apparent in roentgenogram after 16 mo.	Syphilis acquired by blood transfusion; no marked constitutional reaction

Burrows [10]	1937	White ♂	28	+	—	+	+	Humerus; skull; radius; ulna; fibula	Osteoperiostitis	None	15 mo. after primary	None given after fracture; spontaneous healing	Pathologic fracture of humerus; other lesions asymptomatic and discovered on routine roentgen ray examination
Newman and Saunders [11]	1938	White ♀	28	—	+	..	+	Skull; radius; ulna; humerus; tibia	Osteomyelitis	Severe myopathy; anemia	After secondary	Asymptomatic improvement after 4 injections of a bismuth compound, complete healing apparent in roentgenogram after 4 mo. treatment	Marked constitutional reaction, with myopathy and anemia, clearing with antisyphilitic treatment
Farina [12]	1939	White ♂	29	+	+	N	+	Radius; ulna; skull; sternum; bones of hands and feet	Osteoperiostitis; osteitis	Cutaneous relapse; chancre redux; anemia	5 mo. after primary; return with cutaneous relapse	Symptomatic improvement; relapse; cure with further treatment; arrest apparent in roentgenogram after 2 wk.	Return of symptoms with secondary eruption and chancre redux; widespread lesions
Squires and Weiner [13] (a)	1939	White ♀	20	—	+	—	+	Skull	Osteoperiostitis	None	27 days before secondary	Herxheimer reaction positive; improvement visible in roentgenogram 10 wk. later; complete healing apparent 9 mo. later	Husband had early syphilis, with chancre and macular syphilid
(b)	1939	White ♀	49	—	+	..	+	Ulna	Osteoperiostitis	None	Not stated	Complete healing after 5 injections of a bismuth compound and 5 injections of neoarsphenamine	Patient had condylomata lata and mucous patches, with a papulosquamous syphilid
Wile and Welton [14] (a)	1940	White ♂	33	+	—	—	+	Ribs; spine	Osteomyelitis	Alopecia; splenomegaly	4 mo. after primary	Symptomatic improvement after 6 injections of arsphenamine and a bismuth compound combined; complete healing apparent in roentgenograms 9 yr. later	Lesions resembling those of multiple myeloma; constitutional symptoms marked; symptoms followed 6 injections of arsphenamine; biopsy
(b)	1940	White ♀	23	+	+	..	+	Skull	Osteoperiostitis; focal osteomyelitis	Splenomegaly	About 1½ mo. after primary	Herxheimer reaction positive; rapid symptomatic improvement; roentgenograms normal 4 yr. later	No marked constitutional reaction; severe headache
Pian and Frazier [23]	1940	Chinese ♂	8	—	+	..	+	Skull; tibia; fibula; humerus; radius; ulna	Osteomyelitis	None	5 wk. after blood transfusion	Herxheimer reaction; symptoms gone after 2 injections of neoarsphenamine; healing apparent in roentgenograms 2 mo. later	Kala-azar; syphilis acquired by blood transfusion; *S. pallida* recovered from blood

"no physician, however well versed in the art, is capable of stating whether a given tumefaction is a lesion of the periosteum or of the bone itself."

Although based on clinical observations alone, without benefit of roentgenography, the writings of Mauriac,[3] Lancereaux[4] and Wile and Senear[5] afford valuable clinical data on the frequency and the course of early osseous syphilis in general.

Supported by gross and microscopic postmortem evidence, the case report of Lancereaux[4] is perhaps the first accurate description of destructive osteitis in early syphilis. In this remarkable case, destructive lesions of the nasopalatine and the frontal bones supervened one year after the development of a labial chancre and characteristic manifestations of secondary syphilis (rash, mucous patches and alopecia). So extensive were the osseous changes that death from brain abscess occurred after perforation of the inner table of the skull. Microscopically, dissolution of bone and dense round cell infiltration were noted.

Since the introduction of the roentgen examination into clinical medicine, more and more case reports of destructive bone lesions in early syphilis have been recorded.[6] In surveying the available literature, we have been able to collect 15 cases, which are summarized in tabular form (table 1).

The case reports of Nitchew[7] are the first recorded observations to be supported by roentgenologic proof of bone destruction. This author expressed the belief that his 3 cases represented "precocious tertiary accidents," and, since in all 3 instances the onset of symptoms followed treatment with neoarsphenamine, he suggested that the arsenical therapy had altered the invasiveness of the spirochetes. In the same year Gougerot, Mathieu and Jais[8] reported a case in which pathologic fracture of the clavicle occurred forty days after the secondary eruption.

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3. Mauriac, C.: Sur les affections syphilitiques précoces du système osseux, Gaz. d. hôp. **45**:739, 1872.

4. Lancereaux, E.: Les ostéites syphilitiques, Ann. de dermat. et syph. **7**:261, 1886.

5. Wile, U. J., and Senear, F. E.: A Study of the Involvement of the Bones and Joints in Early Syphilis, Am. J. M. Sc. **152**:689, 1916.

6. It is of some interest in this connection that roentgenographically demonstrable bone lesions are not infrequent in the early stages of yaws, having been observed in 15 per cent of cases in one series (Turner, T. B.; Saunders, G. M., and Johnston, H. M.: Annual Report of the Jamaica Yaws Commission, Kingston, Jamaica, 1932).

7. Nitchew, L.: A propos des ostéo-périostites syphilitique précoces, Ann. d. mal. vén. **27**:600, 1932.

8. Gougerot, Mathieu and Jais: Fracture spontanée de la clavicule au début de la syphilis secondaire, Ann. d. mal. vén. **27**:31, 1932.

TABLE 2.—*Summary of Cases from Johns Hopkins Hospital*

Patient			Evidence of Early Syphilis				Bone Lesion		Associated Lesions and Conditions	Relation of Bone Lesion to Primary or Secondary Syphilis	Effect of Specific Treatment	Comment
	Race, Sex	Age, Yr.	Primary	Secondary	Darkfield Examination	Serologic Reaction	Bone Involved	Type of Involvement				
A. S.	White ♀	23	—	+	..	+	Tibia; fibula	Osteoperiostitis	Polyarthritis; serologic relapse; hepatitis	14 mo. after secondary	Relief after 6 injections of arsphenamine	Osseous lesions developed with serologic and hepatic recurrence after lapse following inadequate treatment
E. T.	Negro ♀	20	—	+	..	+	Humerus	Osteomyelitis	Polyarthritis	8 wk. before secondary	Improvement after injection of arsphenamine; complete relief after 8 injections	Serologic reversal after 4 injections of arsphenamine; complete healing apparent in roentgenograms after 4 mo. of treatment
J. C.	Negro ♂	35	+	+	..	+	Sternum	Osteoperiostitis	Asymptomatic syphilis of the central nervous system; orchitis	2 wk. after secondary	Improvement after 7 injections of arsphenamine; relapse also healed promptly	Trauma during secondary syphilis; lesion returned during treatment lapse
C. B.	Negro ♀	24	—	+	..	+	Skull	Osteoperiostitis	None	Before secondary	Improvement after 1 injection of arsphenamine	Serologic reversal after 5 mo. of treatment
A. T.	Negro ♂	24	—	+	..	+	Tibias	Osteoperiostitis	None	With secondary	Relief after 2 injections of arsphenamine	Follow-up observation incomplete
H. W.	Negro ♀	21	—	+	..	+	Skull	Osteitis	None	?	"Prompt relief"	Serologic reversal after 6 injections of neoarsphenamine; roentgenograms and physical findings normal after 7 yr.
A. W.	Negro ♀	17	..	+	..	+	Clavicle	Osteitis	Polyarthritis	1 mo. after secondary	Relief after 1 injection of arsphenamine	Subacute salpingitis; serologic tests negative and physical findings normal after 5 yr.; complete healing evident in roentgenograms
A. G.	Negro ♂	39	+	+	..	+	Skull	Osteoperiostitis	Arthralgia; iritis	With secondary	Relief after 3 injections of arsphenamine	Follow-up observation incomplete
G. N.	White ♂	25	—	+	+	+	Skull	Osteoperiostitis	None	11 wk. before secondary	Relief after 6 injections of neoarsphenamine	Extragenital chancre (?); secondary lesions developed during arsenical treatment; follow-up observation incomplete
G. R.	White ♂	35	+	—	..	+	Nasal bones	Osteitis	Anemia; polyarthritis	15 mo. after primary	Gradual healing after intensive treatment, including malaria	Malignant syphilis; marked constitutional reaction; episodes of leukopenia and agranulocytosis; biopsy
W. J.	Negro ♂	24	+	+	..	+	Skull	Osteoperiostitis	Arthralgia; uveitis	With secondary	Relief after 1 injection of arsphenamine	Follow-up observation incomplete
R. S.	Negro ♀	22	—	+	+	+	Skull	Osteoperiostitis	Arthritis of temperomandibular joint	5 wk. before secondary	Relief after 4 injections of arsphenamine	History of trauma; development of jaundice during arsphenamine treatment; roentgenogram normal 10 mo. later
S. B.	Negro ♀	36	—	+	..	+	Humerus; clavicle	Osteoperiostitis	None	?	Relief after 1 injection of arsphenamine	History of trauma; serologic reversal after 6 injections of arsphenamine
E. D.	Negro ♀	38	—	+	..	+	Clavicle	Osteoperiostitis	None	With secondary	Relief after 5 injections of neoarsphenamine	Follow-up observation incomplete
F. L.	White ♂	27	+	—	..	+	Facial bones; palate	Osteitis	Alopecia	8 mo. after primary	Gradual healing after intensive treatment	Malignant syphilis; treatment started during primary stage when serologic tests negative; progression during malaria; biopsy

In the case reported by Bloom,[9] symptoms also became manifest after the institution of antisyphilitic treatment. Symptomatic relief and demonstrable healing by roentgen rays followed further treatment. In retrospect, the case reported by Tauber and Goldman[10] as one of "syphilitic anemia with diffuse osteitis and superinfection" seems more probably an instance of skeletal involvement and anemia complicating early syphilis.

Newman and Saunders[11] emphasized the fact that marked constitutional evidences of toxicity may be present in association with early skeletal involvement. In the case they reported the patient, in addition to widespread bone lesions, had severe myopathy and anemia. Farina,[12] also, stressed the debilitating effect of the "malignant" type of early syphilis which developed in the patient whose case he reported.

The recent reports of Squires and Weiner[13] and Wile and Welton[14] indicated that toxemia is not an invariable component of the condition. In both these articles the diagnostic difficulties were stressed and the frequency with which the bones of the skull are involved was noted.

Our own series of 15 cases is also presented in tabular form (table 2). Illustrative case reports and roentgenograms are appended.

ANALYSIS OF CASES

An accurate estimate of the frequency of early skeletal syphilis is difficult to make. That it is more common than is generally recognized was demonstrated clinically by Wile and Senear.[5] These authors carefully examined 165 patients with primary and secondary syphilis for objective skeletal abnormalities and were able to detect evidences of bone or joint involvement in 60, or 36 per cent, of the total. Many of these changes were minimal and would have been missed by a casual examiner. Their study gives no indication of the frequency with which destructive lesions were present, but it seems highly probable that if roentgenologic examination of the skeleton was included in such a study, instances of osteolytic processes would be noted.

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9. Bloom, P.: Destructive Osteitis and Facial Paralysis in Secondary Syphilis, Arch. Dermat. & Syph. **29**:940 (June) 1934.

10. Tauber, E. B., and Goldman, L.: Syphilitic Anemia with Diffuse Osteitis and Superinfection, Am. J. Syph. & Neurol. **19**:339, 1935.

11. Newman, B. A., and Saunders, H. C.: Skeletal System Manifestations During Secondary Syphilis, New York State J. Med. **38**:788, 1938.

12. Farina, A.: Su un caso di osteomielite gummosa nel periodo precoce della lue, Gior. di med. mil. **87**:59, 1939.

13. Squires, J. B., and Weiner, A. L.: Osteitis in Early Syphilis: Report of a Case, Arch. Dermat. & Syph. **39**:830 (May) 1939.

14. Wile, U. J., and Welton, D. G.: Early Syphilitic Osteomyelitis with a Report of Two Cases, Am. J. Syph., Gonor. & Ven. Dis. **24**:1, 1940.

The average age of the patients in both series was 27.9 years, a figure slightly higher than the age incidence for early syphilis in general.[15] Sex was not a factor in predisposing the patient to early osseous involvement, for the number of males and females was equal. In 11 of our 15 cases the condition occurred in Negroes, a ratio in keeping with the race distribution of our general clinic population.[16]

The bones of the skull are most frequently affected, the frontal, the parietal and the nasopalatine bones seeming especially vulnerable. The sternoclavicular region ranks next in order of frequency. The long bones are more rarely involved, more often in the lower extremity than in the upper. It is usual for the overlying periosteum to be involved when an area of bone is diseased. Occasionally, osteitis occurs without palpable or roentgenographically visible periosteal reaction. Osteomyelitis is the least common lesion, although involvement of the medullary cavity may be difficult to ascertain.

Pain and localized tumefaction are the cardinal symptoms of destructive bone lesions, in many cases completely overshadowing the other manifestations of early syphilis. The pain varies markedly in intensity, its severity seemingly being dependent on the degree of associated periostitis, and is worse at night. It should be noted, however, that at times lesions may be completely asymptomatic and are discovered only when the finding of one lesion prompts the clinician to make roentgenographic study of other portions of the skeleton. Stokes and Garver,[17] in a tabulation of the symptoms of early constitutional syphilis, have called attention to the frequency of the complaint of headache, which they noted in 24 per cent of their patients. Localized headache is an important symptom of destructive osseous lesions which involve the skull and is at times so severe that the possibility of acute syphilitic meningitis must be excluded. Tumefaction, indicative of concomitant periosteal involvement, is in no way different from that which occurs when periostitis alone is present. Tenderness, with little or no reddening or local production of heat, is the rule. In rare instances localized areas of bone depression may be noted.

The onset of symptoms may precede or follow the secondary eruption. In 4 of our cases osseous involvement was evident before the rash appeared. In 2 others (cases 10 and 15) secondary manifesta-

15. Padget, P.: Long Term Results in the Treatment of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **34**:692, 1940.

16. Turner, T. B.: The Race and Sex Distribution of the Lesions of Syphilis in Ten Thousand Cases, Bull. Johns Hopkins Hosp. **46**:159, 1930.

17. Stokes, J. H., and Garver, V. C.: Modern Clinical Syphilology, ed. 2, Philadelphia, W. B. Saunders Company, 1936, p. 686.

tions were absent. Interestingly enough, in both of these cases the patients received treatment during the primary stage and in both extensive necrosis of the nasopalatine bones developed. The nature of the lesions in these 2 cases indicates that severe osseous relapse may complicate the treatment of early syphilis. That osseous lesions may appear after considerable antisyphilitic treatment has been recorded previously by Nitchew, Farina and Burrows.

The type of secondary eruption cannot be correlated with the extensiveness of the bone changes. Macular and maculopapular eruptions predominated in our series. No rupial or ecthymatous syphilides were noted.

The most frequently associated condition is arthritis, usually involving several joints, which responds rapidly to antisyphilitic treatment. We have noted involvement of the central nervous system only once. More often than not, a marked constitutional reaction is absent. Occasionally, as in our cases 10 and 15, and in those reported by other authors,[18] the patient is markedly ill, with fever, anemia, weakness, loss of weight and other evidences of toxemia.

The response to treatment is favorable. A Herxheimer reaction may follow the initial injection of an arsenical, but the pain is promptly relieved and associated periosteal reactions subside rapidly. In only 2 of our cases could the condition be described as malignant or treatment resistant. In these 2 remarkable cases (10 and 15) heroic measures were required to effect a cure.

In the usual course of events, the bone lesions heal promptly, leaving no residual evidence of their existence; serologic tests are reversed as promptly as in cases of uncomplicated early syphilis, and no late sequelae become manifest.

We have noted no instances of pathologic fracture resulting from early syphilitic osteitis. Saraceni [19] has recorded such an accident. In the case reported by Gougerot, Mathieu and Jais,[8] fracture occurred at the inner third of the clavicle, a common site of involvement. The interpretation of the case reported by Burrows [20] may be questioned, since the fracture, together with diffuse osteolytic lesions, occurred after serologic reversal and all lesions healed spontaneously, without further antisyphilitic treatment.

None of our patients acquired syphilis by blood transfusion. That severe osteomyelitis may dominate the picture of syphilis acquired in

18. Newman and Saunders.[11] Farina.[12] Squires and Weiner.[13]

19. Saraceni, G.: Febbre, frattura spontane e pigmentazione sifilitica, Gazz. med. di Roma **35**:421, 1909.

20. Burrows, H. J.: Pathological Fracture of the Humerus Complicating Late Secondary Syphilis, Brit. J. Surg. **24**:452, 1937.

this manner has been demonstrated by Mandelbaum and Saperstein [21] and by Pian and Frazier.[22]

PATHOLOGIC ASPECTS

Syphilis long has been known as "the great bone former," and certainly osteoplastic features are outstanding in the bone lesions of late syphilis. In the early stages of the disease, however, the fundamental process is one of osteolysis, with replacement by syphilitic granulation tissue.

Biopsy reports are included in the articles by Tauber and Goldman [10] and Wile and Welton,[14] and to these now may be added two

Fig. 1 (case 15).—Photomicrograph of nasal tissue taken for biopsy. Destruction of the bone is apparent, with round cell infiltration most marked around the blood vessels; × 100.

from the present series. One autopsy report, that of Lancereaux, is available. Necrosis of bone with ingrowth of round cells is the feature common to all these reports.

21. Mandelbaum, H., and Saperstein, A. N.: Transmission of Syphilis by Blood Transfusion: A Case of Acute Gummatous Osteomyelitis, J. A. M. A. **106**:1061 (March 28) 1936.

22. Pian, H. C., and Frazier, C. N.: Transfusion Syphilis with Widespread Osteomyelitis and Cutaneous Lesions of an Erythema Multiforme Type, Chinese M. J. **57**:301, 1940.

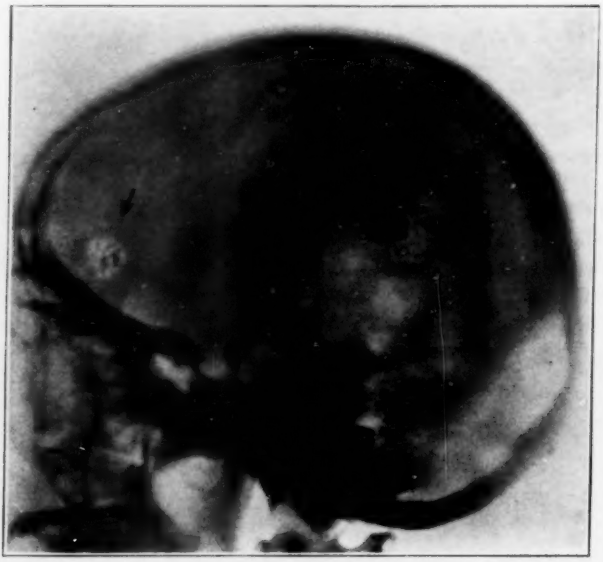

Fig. 2 (case 8).—A moth-eaten area of destruction is visible in the frontal bone.

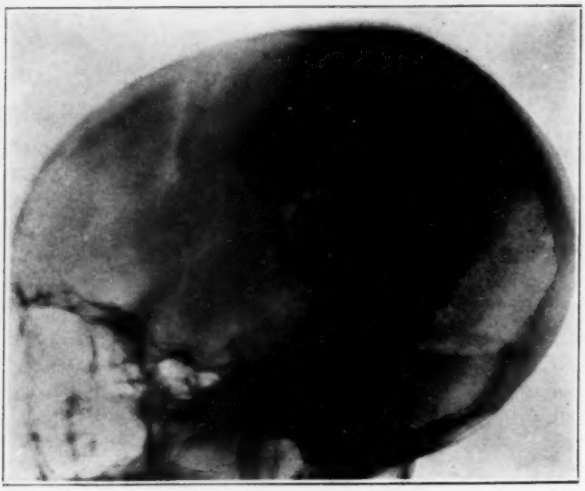

Fig. 3 (case 12).—A circumscribed area of destruction is apparent in the parietal bone.

ROENTGENOLOGIC ASPECTS

In roentgenograms the lesions of the skull are characteristic, consisting of irregularly circular areas of decreased density having a moth-eaten appearance. The thinner and more porous bones of the calvarium are the ones commonly affected, and lesions are rare posterior to the lambdoidal suture. Elsewhere, the bony changes are less diagnostic, although involvement about the sternoclavicular joint is suggestive.

Swelling of soft tissue or wavy periosteal markings parallel to the surface of the bone are indicative of concomitant periostitis. The presence of medullary involvement can be inferred when the osteolytic process is noted to involve the inner portion of the cortex or (rarely) when sequestration can be detected as healing progresses.

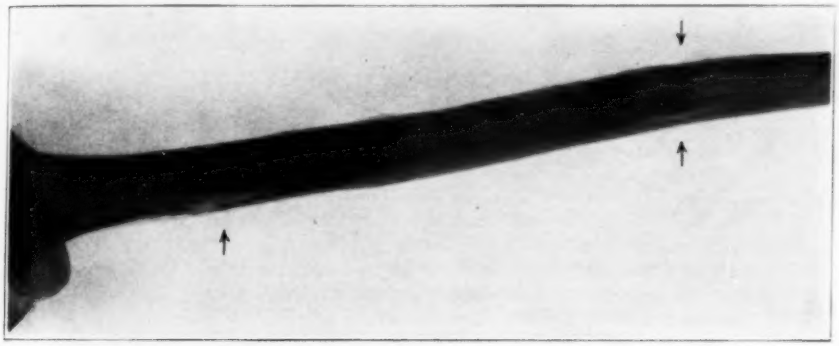

Fig. 4 (case 2).—Spotty areas of osteolysis are visible in the shaft of the humerus.

Early osseous syphilis must be differentiated most frequently from pyogenic osteomyelitis, tuberculous osteitis and multiple myeloma. Osteitis fibrosa cystica, Hodgkin's disease, leukemic infiltrations, actinomycosis, blastomycosis, coccidioidal granuloma, post-traumatic fibrous osteitis, xanthomatosis, neurofibromatosis and metastases of osteolytic carcinoma more rarely enter into the differential diagnosis.

Discussions of the roentgenographic features of early skeletal syphilis are available in the writings of Stewart [23] and Pancoast, Pendergrass and Schaeffer.[24]

23. Stewart, D. M.: Roentgenological Manifestations of Bone Syphilis, Am. J. Roentgenol. **40**:215, 1938.

24. Pancoast, H. K.; Pendergrass, E. P., and Schaeffer, J. P.: The Head and Neck in Roentgen Diagnosis, Springfield, Ill., Charles C. Thomas, Publisher, 1940, pp. 177-180.

SUMMARY AND CONCLUSIONS

Destructive osseous lesions (osteitis, osteoperiostitis and osteomyelitis) may occur during the early period of syphilis. Fifteen cases from this clinic are presented and, with 15 others gathered from the literature, are analyzed.

The bones of the skull (frontal, parietal and nasopalatine) are most often involved. The sternoclavicular region is not infrequently affected. The long bones are more rarely attacked.

Destruction of the deeper skeletal structures may precede or follow the secondary eruption or may occur as the only manifestation of relapsing early syphilis.

The prompt response to appropriate therapy and the ultimately favorable serologic and clinical outcome indicate that involvement of the deeper skeletal structures adds little to the gravity of early syphilis, with a few notable exceptions.

The pathologic and roentgenographic features of the condition are discussed.

REPORT OF ILLUSTRATIVE CASES

CASE 6.—H. W., an obese Negress aged 21, was admitted to the Syphilis Division on Oct. 6, 1928, complaining of severe headaches of one month's duration. These headaches were continuous but worse at night, so that she was kept awake. Most of the pain was referred to the frontal and left parietal regions.

She appeared well developed and well nourished. There were several annular, scaly, pea-sized papules on the upper lip and typical condylomata lata on the external genitalia. No local tenderness or bony irregularity was noted over the skull. The remainder of the physical examination revealed nothing abnormal.

Serologic tests for syphilis were strongly positive. A roentgenogram of the skull showed circumscribed areas of osteitis in the left frontal bone. The spinal fluid was normal.

Antisyphilitic treatment resulted in prompt symptomatic relief. The patient received ten injections of neoarsphenamine (0.7 Gm. each) and six injections of bismuth subsalicylate (0.2 Gm. each), after which she became delinquent. Serologic tests for syphilis became negative after six injections of neoarsphenamine and remained negative.

A follow-up examination was made Feb. 2, 1935. She had continued to feel well, and the physical examination revealed no evidence of syphilis. Serologic tests for syphilis were negative. Another roentgenogram of the skull showed an area of increased density in the left frontal bone, with a small area of rarefaction in the center, compatible with a diagnosis of healed osteitis.

CASE 12.—R. S., a Negress aged 22, was admitted to the General Medical Clinic on Oct. 16, 1935, complaining of pains in the head and chest. One month previously she had struck her head against a door, but had experienced no persistent pain until one week before admission. Examination at this time revealed a firm, rounded, slightly tender tumefaction over the right temporal bone. There was also tenderness over the right frontal bone and over the body of the sternum. Pain in the right temporomandibular joint resulted when the jaws were clenched. The genitalia, skin and mucous membranes were normal. A roentgenogram showed

moth-eaten areas of bone destruction, without evidence of new bone formation, in the right frontal and temporal bones. Serologic tests for syphilis were positive.

The patient returned six weeks later, complaining not only of cephalalgia but of a severe sore throat and a cutaneous rash, both of two weeks' duration. She was referred to the Syphilis Division, where physical examination showed a diffuse scaly maculopapular eruption over the trunk, an injected pharynx and four moist, flat-topped papules on the labia, material from which was positive for Spirochaeta pallida on dark field examination. She did not appear acutely ill or malnourished. The skeletal abnormalities previously noted were unchanged. The remainder of the physical examination revealed nothing abnormal.

Treatment with arsphenamine was started immediately. After four injections symptomatic relief was complete, but jaundice developed as a result of administration of the drug. Two months later treatment was resumed with neoarsphenamine, and in the following eighteen months she received thirty-one injections of neoarsphenamine (0.6 Gm. each) and twenty-eight injections of bismuth subsalicylate (0.2 Gm. each). Reversal of the serologic reactions was achieved wtihin five months and was maintained. A roentgenogram taken Aug. 19, 1936 showed complete healing of the bone lesions. The spinal fluid examined on August 26 was negative for S. pallida. Complete physical examination on Aug. 4, 1938 revealed no clinical evidence of syphilis.

CASE 15.—F. L., a white salesman aged 27, noticed the development of a penile lesion in July 1939. Dark field examination was not done, but serologic tests for syphilis were negative. On clinical grounds alone antisyphilitic treatment was started elsewhere and 12 intravenous injections given, together with inunctions of mercury. Despite this treatment, the penile lesion did not heal, and the patient was hospitalized in Atlanta, Ga. Here a 3 plus Wassermann reaction of the blood was reported. Under further antisyphilitic treatment and local applications the lesion slowly healed.

After eight months of regular antisyphilitic treatment, and during a course of bismuth therapy, a painful nodular swelling developed on the hard palate, which gradually progressed, eventually destroying the palate.

He was admitted to the Johns Hopkins Hospital on June 18, 1940. At this time, he appeared seriously ill and grossly undernourished. There was diffuse, patchy alopecia. The central portion of the hard palate was destroyed over an area 6 cm. in diameter. The nasal bones above the palate were destroyed, and it was possible to look upward as far as the base of the skull. One centimeter behind the glans penis was an indurated scar encircling the shaft. The remainder of the examination revealed nothing abnormal.

The results of flocculation tests for syphilis were positive, and there was 80 to 90 units of reagin in the blood as determined by quantitative titration. A roentgenogram showed destruction of the bones of the face, particularly in the region of the hard palate. The calvarium was normal. The spinal fluid was negative for organisms. A biopsy specimen was removed from the nose. Microscopic study showed ulceration of the stratified squamous epithelium, areas of bone destruction and heavy infiltration of mononuclear inflammatory cells, especially about the blood vessels.

The patient was inoculated with tertian malaria and had a course of twelve satisfactory paroxysms, with a temperature of 105 F. or over. During the course of the malaria, however, the lesion in the nasopharynx did not heal but expanded to involve more of the palate and the maxilla.

In an effort to control the situation, the patient was given massive arsenical treatment with mapharsen. He received 90 mg. of the drug in three divided doses the first day and 160 mg. a day in four doses for the next three days. Simultaneously he was given 15 Gm. of potassium iodide per day, but the latter medication was discontinued when pustular iododerma developed. Sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) powder was applied locally to the nasopharynx to prevent secondary infection.

This intensive treatment resulted in relief of pain and dramatically prompt healing of the nasal lesion. The patient was fitted with a dental prosthesis and advised to continue regular antisyphilitic treatment. Since then he has received alternate courses of mapharsen and a bismuth compound in the usual therapeutic doses and has remained well.

Progress in Internal Medicine

DISEASES OF NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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Advances in the field of nutrition in the past have been of interest only to a limited few. Since the recent national emergency, however, advances in this field have become of great importance to every one. The potential necessity of limitation of buying power makes it now important that every one be acquainted with what and how much food constitutes a well balanced diet. A national campaign to inform the public in this direction already has begun.

Studies of vitamins and other essential nutrient substances during the past year have been most actively conducted. The general recognition and acceptance of the conception that deficiency of vitamins usually is multiple rather than single is encouraging. The close relation between the liver and metabolism of vitamins again has been emphasized, and important advances in this direction have been accomplished.

VITAMIN A

Chemical and Physiologic Properties.—During 1941 there has been an unusually large number of extensive physiologic studies on vitamin A. Some of the most interesting have been those concerned with the effects of vitamin A on the skeletal system of animals. In the 1940 review of nutrition [1] the work of several authors was reported in which it was found that after certain animals subsisted on diets deficient in vitamin A widespread degeneration of the central and peripheral nervous systems developed. It was suggested that these changes were due directly to the

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1. Butt, H. R., and Leary, W. V.: Diseases of Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **67**:411-465 (Feb.) 1941.

destructive effects of vitamin A deficiency on the nervous system. Recent papers by Mellanby [2] and Wolbach and Bessey,[3] however, bring out the inference that one of the main functions of vitamin A is to influence the structure of growing bone. It is stressed that this function is accomplished, perhaps, by limitation of the number and the degree of activity of osteoblasts and osteoclasts. Mellanby has shown that in the growing dog osteoblastic and osteoclastic activity is increased, with resulting proliferation of cancellous bone at the expense of compact bone. Thus, many bones lose their normally fine molding and outlines and become somewhat thickened and enlarged; some of the main zones where such overgrowth of bone occurs are in the skull and the vertebral column. Apparently, these overgrowths of bone are related to degenerative changes in the brain and in cranial and peripheral nerves. The bony overgrowth and the degenerative changes in nerves are greatest in the cervical region of the spinal cord, but the anterior and posterior root ganglions of the spinal cord also may be compressed and the nerve fibers destroyed by overgrowth of the vertebral bone. This evidence suggests that changes in the nervous system which formerly were thought to be the direct results of deficiency of vitamin A actually were results of overgrowth of bone in the vicinity of the affected nerves and nerve cells and of pressure effects resulting therefrom. It has also been demonstrated that in cattle fed rations deficient in vitamin A there develops an increase in the pressure of the cerebrospinal fluid. This also is said to be a result of bony overgrowth and pressure on the ventricles.[4] Organic changes resulting from bony overgrowth in the ear also have been reported.[5] The necessity of vitamin A in the normal growth of teeth also has been stressed in two extensive studies.[6]

In recent investigations the role of the liver in the storage of vitamin A continues to be emphasized. In a study by Ralli and her asso-

2. Mellanby, E.: Skeletal Changes Affecting the Nervous System Produced in Young Dogs by Diets Deficient in Vitamin A, J. Physiol. **99**:467-486 (June 30) 1941.

3. Wolbach, S. B., and Bessey, O. A.: Vitamin A Deficiency and the Central Nervous System, Am. J. Path. **17**:586 (July) 1941.

4. Moore, L. A., and Sykes, J. F.: Terminal Cerebrospinal Fluid Pressure Values in Vitamin A Deficiency, Am. J. Physiol. **134**:436-439 (Sept.) 1941.

5. Perlman, H. B., and Willard, J.: The Ear in Experimental Vitamin A Deficiency, Ann. Otol., Rhin. & Laryng. **50**:349-362 (June) 1941.

6. Burn, C. G.; Orten, A. U., and Smith, A. H.: Changes in the Structure of the Developing Tooth in Rats Maintained on a Diet Deficient in Vitamin A, Yale J. Biol. & Med. **13**:817-830 (July) 1941. Schour, I.; Hoffman, M. M., and Smith, M. C.: Changes in the Incisor Teeth of Albino Rats with Vitamin A Deficiency and the Effects of Replacement Therapy, Am. J. Path. **17**:529-562 (July) 1941.

ciates [7] specimens of the livers of 25 healthy persons killed in accidents and 91 other subjects who had suffered from various diseases were obtained at necropsy, in most cases within twenty-four hours after death. These authors accepted the hypothesis that the normal liver contains at least 40,000 U. S. P. units of vitamin A per hundred grams of hepatic tissue. If this content is accepted as constituting a normal value, then it is seen that there is a striking reduction in the concentration of vitamin A in the livers of patients who have cirrhosis or acute infection. Also, on the basis of study of material obtained at necropsy, Ahmad and Seshan [8] reported that the average reserve of vitamin A in the liver in persons of the working class in India is between 7 and 10 micrograms per gram of hepatic tissue.

The particular site of storage of vitamin A in the liver has always been debatable. Cox [9] suggested that vitamin A is stored in the Kuppfer cells. Other zones of storage have been suggested by Popper and his associates.[10]

That the liver is intimately connected with vitamin A metabolism cannot be denied. Horton and his co-workers [11] have shown that when vitamin A was not included in the diet of rats the concentration of the vitamin in the blood and the liver declined in seeming ratio to the deficiency. They pointed out that a normal concentration of the vitamin in the blood cannot be maintained unless there is adequate storage of it in the liver and that therefore as the liver stores are depleted the concentration in the blood gradually decreases. Complete absence of vitamin A occurs at about the same time in the blood and in the liver. A conception of the manner in which vitamin A is mobilized from its reserves is provided by the work of Young and Wald.[12] These authors

7. Ralli, E. P.; Papper, E.; Paley, K., and Bauman, E.: Vitamin A and Carotene Content of Human Liver in Normal and in Diseased Subjects: An Analysis of One Hundred and Sixteen Human Livers, Arch. Int. Med. **68**:102-111 (July) 1941.

8. Ahmad, B., and Seshan, P. K.: Vitamin A and Carotene Reserves in Human Livers, Indian M. Gaz. **76**:156-157 (March) 1941.

9. Cox, A. J.: Site of Vitamin A Storage in the Liver, Proc. Soc. Exper. Biol. & Med. **47**:333-335 (June) 1941.

10. Popper, H., and Greenberg, R.: Visualization of Vitamin A in Rat Organs by Fluorescence Microscopy, Arch. Path. **32**:11-32 (July) 1941. Popper, H., and Ragins, A. B.: Histologic Demonstration of Vitamin A in Tumors, ibid. **32**:258-271 (Aug.) 1941. Popper, H.: Histologic Distribution of Vitamin A in Human Organs Under Normal and Under Pathologic Conditions, ibid. **31**:766-802 (June) 1941.

11. Horton, P. B.; Murrill, W. A., and Curtis, A. C.: Vitamin A and Carotene: I. The Determination of Vitamin A in the Blood and Liver as an Index of Vitamin A Nutrition of the Rat, J. Clin. Investigation **20**:387-393 (July) 1941.

12. Young, G., and Wald, G.: The Mobilization of Vitamin A by the Sympathico-Adrenal System, Am. J. Physiol. **131**:210-215 (Nov.) 1940.

observed that excision of a lobe of the liver in the rabbit results in decreases of about 25 per cent in the vitamin A content and 50 per cent in the carotene content of the remaining part of the organ. At the same time that the lobe of liver is removed, the value for vitamin A in the blood increases to three to seven and a half times the original value. It was also observed that electric stimulation of the splanchnic nerve results in a large increase of vitamin A in the blood and that the intravenous injection of epinephrine causes a similar increase. The authors concluded, therefore, that vitamin A is mobilized from its reserves in the liver by sympathetic-adrenal stimulation, comparable to that which mobilizes sugar and certain plasma proteins.

Again, it has been shown by Sherman [13] that the unsaturated fatty acids interfere with some phase of the metabolism of carotene and of vitamin A. It has been reported [14] that although carotene and xanthophyll are somewhat readily excreted in human feces, it appears that vitamin A is not excreted until the intake reaches a threshold value considerably more than all ordinary dietary levels and that when this threshold value is exceeded the fraction excreted increases with the intake.

Methods of Measuring Vitamin A Deficiency.—Much controversy and confusion continue to be associated with this subject. For physical methods of measuring vitamin A, the reader is referred to several recent reports.[15] Some workers [16] contended that the adaptation to dark test as an index of vitamin A deficiency is inadequate, whereas others [17] expressed the belief that the continued use of the biophotometer in the

13. Sherman, W. C.: The Effect of Certain Fats and Unsaturated Fatty Acids upon the Utilization of Carotene, J. Nutrition **22**:153-165 (Aug.) 1941.

14. Wald, G.; Carroll, W. R., and Sciarra, D.: The Human Excretion of Carotenoids and Vitamin A, Science **94**:95-96 (July 25) 1941.

15. Mattill, H. H.: Fat-Soluble Vitamins, in Luck, J. M., and Smith, J. H. C.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1941, vol. 10, pp. 395-422. Wilkie, J. B.: Physical and Chemical Determination of Vitamin A, Indust. & Engin. Chem. (Analyt. Ed.) **13**:209-211 (April 15) 1941. Peterson, W. J.: Recent Developments in Methods for Determining Carotene, ibid. **13**:212-216 (April 15) 1941. Parker, A. E., and Oser, B. L.: Photoelectric Photometer for Vitamin A Estimation, ibid. **13**:260-262 (April 15) 1941.

16. Dann, W. J., and Yarbrough, M. E.: Dark Adaptometer Readings of Subjects on a Diet Deficient in Vitamin A, Arch. Ophth. **25**:833-838 (May) 1941. Stewart, C. P.: Nutritional Factors in Dark Adaptation, Edinburgh M. J. **48**:217-237 (April) 1941.

17. (*a*) Eckardt, R. E., and Johnson, L. V.: A Comparison of Two Methods of Measuring Dark Adaptation, J. Pediat. **18**:195-199 (Feb.) 1941. (*b*) Jeans, P. C.; Blanchard, E. L., and Satterthwaite, F. E.: Dark Adaptation and Vitamin A: Further Studies with the Biophotometer, ibid. **18**:170-194 (Feb.) 1941.

study of vitamin A deficiency is valid. The recent extensive work of Jeans and his associates [17b] would tend to show that the biophotometer gives rather constant results concerning the status of vitamin A among human beings. Jeans has pointed out that the apparently inconsistent results obtained with his technic by other authors have a logical explanation in the variability of the status of the subjects rather than in the fallibility of the test itself. Subjects in good health with an ample intake of vitamin A react normally to the test at all times. It was observed that the most frequent and usual cause of impaired adaptation seemed to be deficiency in utilization resulting from illness, especially from illness due to infection. Jeans and associates also observed that there was a seasonal incidence of dysadaptation: The greater incidence was found to obtain in the winter; the lesser, in the summer. The authors expressed the belief that seasonal incidence probably is more closely related to infection than to seasonal variations in diet.

Definite correlation between the results of biophotometric tests and the vitamin A content of human blood has not yet been established.[18] In an excellent and extensive study, Josephs and his associates [18b] asked a pertinent question: "What is meant by vitamin A deficiency?" They pointed out that deficiency of vitamin A may be defined as "the state that is reached when the reserves are so reduced that they are unable any longer to prevent changes characteristic of deficiency" or "a state in which the distribution is so interfered with that the tissues are no longer supplied with sufficient vitamin to prevent characteristic changes." They reemphasized that knowledge of the level of vitamin A in the blood is of no value unless it is possible to learn the significance of the level in relation to storage and adequate distribution of the vitamin. The content of vitamin A in the blood has no constant relation to the store of the vitamin. The only conclusion Josephs and his associates reached was that a high value for vitamin A in the blood is inconsistent with deficiency of the vitamin. Although they expressed the belief that adaptation to dark time is definitely related to a poor diet and low content of vitamin A in the blood, yet moderate prolongation of the adaptation time has little diagnostic significance. Therefore, it cannot be said that such prolongation is presumptive evidence that deficiency exists or that moderate prolongation is evidence that mild deficiency exists. In this paper the whole question is dealt with fairly. It should be read by any one interested in the measurement of deficiency of vitamin A.

18. (*a*) Caveness, H. L.; Satterfield, G. H., and Dann, W. J.: Correlation of the Results of the Biophotometer Test with Vitamin A Content of Human Blood, Arch. Ophth. **25**:827-832 (May) 1941. (*b*) Josephs, H. W.; Baber, M., and Conn, H.: Studies in Vitamin A.: Relation of Blood Level and Adaptation to Dim Light to Diet, Bull. Johns Hopkins Hosp. **68**:375-387 (May) 1941.

Kruse [19] suggested that biomicroscopy be employed in the detection of the early ocular changes resulting from vitamin A deficiency. He reported that of 143 persons in a low income group, 45 per cent had gross and 54 per cent had microscopic ocular lesions (xerosis conjunctivae) characteristic of avitaminosis A. The author suggested that xerosis probably precedes night blindness as an early sign of deficiency of vitamin A. Kruse recommended biomicroscopic examination as a simple, convenient objective method; when it is combined with gross examination all degrees of xerosis may be graded according to severity and extent. He suggested that this condition is relatively prevalent in the population at large. He also pointed out that the vascular reaction in the eyes of patients with vitamin A deficiency is distinct from that noted in the eyes of patients with ariboflavinosis.

Role of Vitamin A in Health and Disease.—Lathyrism is a disease caused by subsistence on a diet composed predominantly of a species of pea (Lathyrus cicera). The disease occurs during famine, especially in India and northern Africa, when the poorer classes of the population are reduced to subsistence on a diet composed largely of lathyrus peas. When the crop of wheat, barley and other cereals is poor, the ingestion of peas as the chief article of food for two or three months is sufficient to precipitate the disease in epidemic form. In a recent report from the department of medicine, Peiping Union Medical College, Peiping, China, Frazier and Tsao [20] stated that lathyrism is related to vitamin A deficiency rather than to the effects of a toxin contained in the legume. This disease is characterized clinically by the sudden onset of weakness of the legs, associated with difficulty in sitting or standing. There is gradually progressive spastic paralysis of the lower extremities, which gives the patient a hesitating, springy gait. The disease is not fatal, but if attacks recur it leaves the patient with muscular atrophy and contractures of the lower extremities. It was formerly thought that this disease was caused by a poisonous substance in the pea itself. Investigators have pointed out that where this disease occurred there was also a high incidence of night blindness and that the addition of eggs or meat to the diet prevented the appearance of the characteristic neurologic symptoms. Frazier and Tsao described a case of lathyrism in which the patient had the cutaneous lesions of vitamin A deficiency; with administration of halibut liver oil rapid and complete healing of the cutaneous lesions occurred, but

19. Kruse, H. D.: Medical Evaluation of Nutritional Status: IV. The Ocular Manifestations of Avitaminosis A, with Especial Consideration of the Detection of Early Changes by Biomicroscopy, Pub. Health Rep. **56**:1301-1324 (June 27) 1941.

20. Frazier, C. M., and Tsao, S. M.: Association of Neuromuscular Symptoms and Cutaneous Lesions in Vitamin A Deficiency, Chinese M. J. **59**:399-415 (May) 1941.

muscular weakness did not abate. Even after fifty-two days of such treatment there was no appreciable return of strength.

Various ocular symptoms resulting from deficiency of vitamin A continue to be described. Sandels and her associates [21] have recently reported on a group of 119 children suffering from follicular conjunctivitis for whom supplementary treatment with vitamin A resulted in cure of the condition. It was pointed out that children who received 25,000 or 38,000 U. S. P. units of vitamin A daily did not recover any more rapidly than did those who received only 13,000 U. S. P. units daily. The authors suggested that a time factor apparently operates which limits the rate of healing of a lesion and that the intake of excessive doses of vitamin A does not increase this rate proportionately. The addition of vitamin D or milk to the diet had no effect on the rapidity of healing. A survey of the diets of these children revealed that in each instance the consumption of a diet which had a vitamin A content below 100 U. S. P. units per kilogram of body weight per day permitted the deficiency to develop, whereas a diet with a vitamin A content in excess of 100 to 160 U. S. P. units per kilogram of body weight per day protected a majority of the children against follicular conjunctivitis. It was suggested by the authors that when diets in which carotene furnishes a large proportion of the vitamin A value are utilized, the addition of 200 to 250 U. S. P. units of vitamin A per kilogram of body weight per day will provide a generous allowance for children between the ages of 6 and 12 years. It has been suggested,[22] further, that keratosis follicularis (Darier's disease) also is a result of deficiency of vitamin A. It is interesting to learn that ocular symptoms resulting from deficiency of vitamin A are not uncommon in Newfoundland and Labrador [23] and that they continue to be common in India.[24]

The importance of the liver in the metabolism of vitamin A has been observed in several clinical conditions. Xerophthalmia and keratomalacia associated with obstructive biliary cirrhosis have been reported.[25]

21. Sandels, M. R.; Cate, H. D.; Wilkinson, K. P., and Graves, L. J.: Follicular Conjunctivitis in School Children as an Expression of Vitamin A Deficiency, Am. J. Dis. Child. **62**:101-114 (July) 1941.

22. Peck, S. M.; Chargin, L., and Sobotka, H.: Keratosis Follicularis (Darier's Disease): A Vitamin A Deficiency Disease, Arch. Dermat. & Syph. **43**:223-229 (Feb.) 1941.

23. Steven, D., and Wald, G.: Vitamin A Deficiency: A Field Study in Newfoundland and Labrador, J. Nutrition **21**:461-476 (May) 1941.

24. Kirwan, E. O'G.; Sen, K., and Biswas, R. B.: Nutrition and Its Bearing on Preventable Blindness and Eye Diseases in Bengal: Preliminary Report, Indian J. M. Research **29**:119-124 (Jan.) 1941.

25. Stone, J. B., and Courtney, R. H.: Xerophthalmia and Keratomalacia Associated with Obstructive Biliary Cirrhosis, Virginia M. Monthly **68**:159-163 (March) 1941.

Woodruff and Wright,[26] using a new photometric test, have demonstrated that a prolonged adaptation to dark time is present in cases of obstructive jaundice. They assumed that this is a result of deficient absorption of vitamin A. That deficiency of vitamin A may result from poor absorption of the vitamin also has been reported in cases of diarrhea [27] and celiac disease.[28] In an extensive report Nylung and With [29] emphasized that perhaps 95 to 100 per cent of the total content of vitamin A in the body is to be found in the liver. It is assumed that the vitamin A content of the liver, therefore, is an index of the saturation of the organism with the vitamin; on the basis of the experience of Nylung and With this assumption seems rather warranted, and it appears that it would be true both under normal and under pathologic conditions. The authors, however, were careful to point out, as have others, that a liver which has a low vitamin A reserve, or even a liver which lacks the vitamin, does not constitute proof that a clinical deficiency of vitamin A exists.

In other reports the effect of vitamin A on the secretion of gastric juice [30] and the use of vitamin A in the treatment of gastric ulcer [31] have been considered. Murrill and associates [32] found that among diabetic patients the average concentration of carotene in the blood was significantly higher than it was among nondiabetic persons, whereas the concentration of vitamin A in the blood remained the same as that of persons without diabetes. A good review of studies on vitamin A from the clinical standpoint has been given by Moore.[33]

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26. Woodruff, M. F. A., and Wright, R. D.: The Diagnosis, Incidence and Treatment of Avitaminosis A and D in Obstructive Jaundice, Australian & New Zealand J. Surg. **10**:135-145 (Oct.) 1940.

27. Goldberg, H. K., and Schlivek, K.: Necrosis of the Cornea Due to Vitamin A Deficiency: Report of a Case, Arch. Ophth. **25**:122-127 (Jan.) 1941.

28. May, C. D., and McCreary, J. F.: The Absorption of Vitamin A in Celiac Disease: Interpretation of the Vitamin A Absorption Test, J. Pediat. **18**:200-209 (Feb.) 1941.

29. Nylung, C. E., and With, T. K.: On the Demonstration of Vitamin A Deficiency in Man, Acta med. Scandinav. **106**:202-228, 1941.

30. Földes, F., and Vajda, G.: Effect of Vitamin A on the Secretion of Gastric Juice in Deficient Hydrochloric Acid Production, Brit. M. J. **1**:317-318 (March 1) 1941.

31. Seelig, S. F.: Treatment of Gastric Ulcer with Vitamin A, Guy's Hosp. Rep. **90**:41-54, 1940-1941.

32. Murrill, W. A.; Horton, P. B.; Leiberman, E., and Newburgh, L. H.: Vitamin A and Carotene: II. Vitamin A and Carotene Metabolism in Diabetics and Normals, J. Clin. Investigation **20**:395-400 (July) 1941.

33. Moore, T.: Vitamin A, Post-Grad. M. J. **17**:52-60 (April) 1941.

VITAMIN B COMPLEX

Chemical and Physiologic Properties.—This interesting complex has continued to receive considerable attention during the past year. Perhaps one of the most interesting studies in this particular field has been work which shows that some relation exists between the development of cancer and cirrhosis in animals and a deficiency of various members of this complex. It has been known for some time that when dimethylaminoazobenzene (butter yellow) is fed to rats subsisting on a diet of wild rice and carrots, cirrhosis and eventual cancer of the liver regularly occur. If the basal diet is supplemented, however, by liver or yeast, the liver of the animal is completely protected against the toxic effects of the chemical. These experiments, originally done by Nakahara and Kinosipa, have been amply confirmed recently by Rhoads [34] and his associates, who have also extended the experiments of the Japanese investigators. In their studies they found that the liver of rats after one hundred and fifty days of subsistence on a basal diet plus butter yellow was always the site of marked cirrhosis and primary cancer. The livers of rats subsisting on the same diets and the same amount of butter yellow, however, were entirely normal as long as 15 per cent of the diet was composed of a certain brand of yeast. It was found that although deficiency of riboflavin rendered the animals more susceptible to the two diseases, lack of this protective power of pure riboflavin suggested that some other deficiency also was present. Subsequently, these authors demonstrated that the ingestion of riboflavin mixed with casein substantially protected rats against cancer of the liver formerly produced by feeding them butter yellow. The authors expressed the belief that the results of these experiments provided proof that toxemia can, in fact, cause a deficiency disease by interfering with the function of the enzyme in which the vitamin acts. Others [35] have shown that spontaneous mammary carcinoma disappeared completely in 30 per cent of treated mice after the intravenous injection of a watery yeast extract. Their studies [35c] showed that pantothenic acid, riboflavin and thiamine alone have no or little effect on the growth of tumors and that yeast alone will

34. Rhoads, C. P.: Physiological Aspects of Vitamin Deficiency, Proc. Inst. Med. Chicago **13**:198-205 (Nov. 15) 1940.

35. (*a*) Lewisohn, R.; Leuchtenberger, C.; Leuchtenberger, R., and Laszlo, D.: Effect of Intravenous Injections of Yeast Extract on Spontaneous Breast Carcinomas in Mice, Proc. Soc. Exper. Biol. & Med. **43**:558-561 (March) 1940; (*b*) The Treatment of Spontaneous Breast Adenocarcinomas in Mice with Extracts of Spleen or Yeast, Am. J. Path. **17**:251-260 (March) 1941. (*c*) Lewisohn, R.; Leuchtenberger, C.; Leuchtenberger, R.; Laszlo, D., and Bloch, K.: Prevention of Tumor Growth (Carcinoma 2163) by Intravenous Injections of Yeast and Vitamins, Science **94**:70-71 (July 18) 1941.

prevent the growth of tumors in only about 20 per cent of cases. However, the tumor-preventing effect of yeast was markedly strengthened by the addition of pantothenic acid or riboflavin to the yeast extract. Addition of thiamine to the extract did not improve the tumor-preventing action.

Cirrhosis of the liver in rats has been produced in a number of different ways. The inhalation of carbon tetrachloride and the ingestion of diets high in fat with large doses of alcohol or the use of diets containing selenium all have been capable of producing a cirrhotic picture in the liver of rats. Rich and Hamilton [36] revived these studies last year when they reported that cirrhosis of the liver could be produced in rabbits by dietary deficiency and could be prevented by the feeding of yeast. Some authors [37] have reported the development of cirrhosis among rats suffering from a dietary deficiency, which was reduced by the administration of choline. The feeding of cystine ameliorated the cirrhosis, but the daily administration of choline or yeast neutralized more or less completely the effects of cystine on the liver. Confirming a long-known clinical fact, Lillie and his associates [38] reported results of experiments which suggested that alcohol constitutes an additional insult to hepatic tissue already injured by dietary deficiency. The authors at the time at which they wrote could make no statement as to the nature of the deficiency or deficiencies in the diet used which permitted or caused the development of hepatic cirrhosis.

Using one of the diets described by Rich and Hamilton,[36] Machella and Maguire [39] were unable to confirm the report made by the first-named two authors. Histologic evidence of hepatic cirrhosis did not develop in their animals, in spite of the fact that the usual signs of deficiency of the vitamin B complex became apparent. The authors suggested that the cirrhotic process in the liver of rabbits noted by Rich and Hamilton might have been due to infection with coccidia.

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36. Rich, A. R., and Hamilton, J. D.: The Experimental Production of Cirrhosis of the Liver by Means of a Deficient Diet, Bull. Johns Hopkins Hosp. **66**:185-196 (March) 1940.

37. Earle, D. P., Jr., and Victor, J.: Cirrhosis of the Liver Caused by Excess Dietary Cystine, J. Exper. Med. **73**:161-172 (Feb.) 1941. György, P., and Goldblatt, H.: Experimental Production of Dietary Liver Injury (Necrosis, Cirrhosis) in Rats, Proc. Soc. Exper. Biol. & Med. **46**:492-494 (March) 1941.

38. Lillie, R. D.; Daft, F. S., and Sebrell, W. H., Jr.: Cirrhosis of the Liver in Rats on a Deficient Diet and the Effect of Alcohol, Pub. Health Rep. **56**:1255-1258 (June 13) 1941.

39. Machella, T. E., and Maguire, E. F.: An Attempt to Produce Hepatic Cirrhosis by a Diet Deficient in Vitamin B Complex, Proc. Soc. Exper. Biol. & Med. **46**:502-507 (March) 1941.

It seems fairly well established [40] that the vitamin B complex plays some role in the metabolism of fat, and most investigators [41] now agree that choline probably is a member of the vitamin B complex.

The relation of the vitamin B complex to the syndrome produced by adrenalectomy [42] and the interrelation between this complex and the anterior lobe of the pituitary body [43] also have received consideration. It has also been reported [44] that the effect of yeast on the increased motility of the gastrointestinal tract apparently is due to the presence of live yeast in the gastrointestinal tract itself.

Methods of Measurement.—Attempts to measure quantitatively the vitamin B complex have met with many difficulties. Recently, Golden [45] has described in some detail intestinal changes seen roentgenologically which he asserted are results of deficiency of the vitamin B complex. It has been observed that the intestines revert to normal after administration of the vitamin B complex. Although the author did not claim these lesions to be specific, he did express the belief that they prove helpful in the search for the cause and relief of obscure abdominal symptoms.

Clinical Deficiencies.—The role of the vitamin B complex in normal nutrition [46] and the syndrome of multiple deficiencies has been well discussed.[47] In an interesting paper Spies and his associates [48] reported

40. Longenecker, H. E.; Gavin, G., and McHenry, E. W.: The Relation of the Vitamin B Complex and Liver and Pancreas Extracts to Fat Synthesis, J. Biol. Chem. **139**:611-620 (June) 1941. McHenry, E. W., and Gavin, G.: The B Vitamins and Fat Metabolism: IV. The Synthesis of Fat from Protein, ibid. **138**:471-475 (April) 1941. Richter, C. P., and Hawkes, C. D.: The Dependence of the Carbohydrate, Fat and Protein Appetite of Rats on the Various Components of the Vitamin B Complex, Am. J. Physiol. **131**:639-649 (Jan.) 1941.

41. György, P., and Goldblatt, H.: Choline as a Member of the Vitamin B_2 Complex, J. Exper. Med. **72**:1-10 (July) 1940. Griffith, W. H.: The Nutritional Importance of Choline, J. Nutrition **22**:239-253 (Sept.) 1941.

42. Clark, W. G.: Vitamin B Complex and Adrenalectomy, Endocrinology **28**:545-554 (April) 1941.

43. Sutton, D. C.: Interrelation Between the Vitamin B Complex and the Anterior Lobe of the Pituitary Gland, South. M. J. **34**:47-51 (Jan.) 1941.

44. Russell, R. A., and Nasset, E. S.: The Effects of Various Vitamin Supplements and of Whole Yeast on the Digestion and Absorption of the Carbohydrate of a Complete Diet, J. Nutrition **22**:287-294 (Sept.) 1941.

45. Golden, R.: The Small Intestine in Vitamin B Deficiency, J. A. M. A. **117**:913-917 (Sept. 13) 1941.

46. Elvehjem, C. A.: The Vitamin B Complex in Normal Nutrition, Nature, London **146**:669-672 (Nov. 23) 1940.

47. Sydenstricker, V. P.: The Syndrome of Multiple Vitamin Deficiency, Ann. Int. Med. **15**:45-51 (July) 1941. Sinclair, H. M.: The Vitamin B Complex, Post-Grad. M. J. **17**:3-12 (Jan.-Feb.) 1941. Jolliffe, N.: Recent Advances in Clinical Applications of the B-Vitamins, J. Am. Dietet. A. **17**:5-11 (Jan.) 1941.

48. Spies, T. D.; Grant, H. M., and Grant, J. M.: Observations on the Effectiveness of a Yeast-Peanut Butter Mixture in Vitamin B Complex Deficiencies: A Progress Report, South. M. J. **34**:159-161 (Feb.) 1941.

that a mixture containing 25 per cent yeast (dried brewers' yeast powder), 67 per cent peanut butter and 8 per cent peanut oil is an inexpensive and palatable food mixture useful for protection against pellagra, beriberi and ariboflavinosis. They found that 2 ounces (59 cc.) or more of this mixture administered daily as a supplement to the diet gradually improved the health of the persons who exhibited subclinical symptoms caused by a suboptimal intake of members of the vitamin B complex and that it retarded and prevented recurrence of these diseases among average malnourished persons living in an area in which deficiency diseases were endemic.

In a report of 21 cases of Wernicke's encephalopathy, Campbell and Russell [49] suggested that both thiamine and nicotinic acid be used in the treatment of this disease syndrome. It seemed likely that this syndrome is a multiple deficiency of constituents of the B complex.

In an excellent and extensive study, Patek and Post [50] reported that the administration of vitamin concentrates to patients who had cirrhosis of the liver provided a greater expectancy of life. Similar results have been obtained by other investigators.[51]

Recently, a syndrome was described by Lepore and Golden [52] which is claimed to be the result of deficiency of the vitamin B complex. Clinically, the syndrome is similar to that well known condition often called the "irritable bowel syndrome." In addition to this, the authors reported that a flat curve for tolerance to dextrose administered orally was obtained and that an abnormally small intestinal pattern was seen roentgenologically. These authors observed that clinical improvement often preceded improvement in the roentgenologic appearance of the small intestine but that within three to four weeks improvement in the small intestine usually was demonstrable. For the results obtained the amount of vitamin B complex administered seemed small. In a discussion of this paper, Sosman pointed out the necessity for hesitation in the matter of formulation of any large number of diagnoses of "vitamin B deficiency" until definite, accurate tests of what this complex really is are available.

Equivocal results have been reported after administration of the vitamin B complex to patients who have lichen planus,[53] acute anterior

49. Campbell, A. C. P., and Russell, W. R.: Wernicke's Encephalopathy: The Clinical Features and Their Probable Relationship to Vitamin B Deficiency, Quart. J. Med. **10**:41-64 (Jan.) 1941.

50. Patek, A. J., Jr., and Post, J.: Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex, J. Clin. Investigation **20**:481-505 (Sept.) 1941.

51. Snell, A. M., and Butt, H. R.: Unpublished data.

52. Lepore, M. J., and Golden, R.: A Syndrome of Deficiency of the Vitamin B Complex, J. A. M. A. **117**:918-923 (Sept. 13) 1941.

53. Burgess, J. F.: The Treatment of Lichen Planus with Vitamin B Complex, Canad. M. A. J. **44**:120-123 (Feb.) 1941.

poliomyelitis [54] and various diseases of the eyes, ears, nose and throat.[55] A good review of this problem has been given recently by Jolliffe.[56]

THIAMINE (VITAMIN B_1)

Chemical and Physiologic Properties.—The role of thiamine in carbohydrate metabolism, and particularly in pyruvate metabolism, continues to be actively studied. It has been shown [57] that after an injection of dextrose in a normal person the content of pyruvate in the blood is elevated and that this elevation reaches a maximum at the end of an hour and returns to the normal fasting range within three hours. It is observed that among those persons who have a deficiency of thiamine the fasting value for pyruvate in the blood is elevated and that the pyruvate curve after the ingestion of dextrose is abnormally elevated and prolonged. Others [58] have pointed out that twenty-nine to thirty-seven days on a thiamine-low diet is not long enough for a significant disturbance to occur in the intermediary carbohydrate metabolism of the normal young adult. These authors took the value for bisulfite-binding substances in the urine as a criterion.

Williams, Mason, Wilder and Smith [59] severely restricted the thiamine intake of 4 human subjects for eighty-eight days and observed, among other metabolic defects, an increase of the bisulfite-binding substances (which include pyruvic acid) in the blood when the subject was in the basal state and abnormally elevated and prolonged time curves for bisulfite-binding substances in the blood after the subject had exercised for three minutes.

Williams and Mason,[60] in a subsequent study of 11 persons whose intake of thiamine was restricted less severely but for a longer period,

54. Helms, K.: Acute Anterior Poliomyelitis and Vitamin B Deficiency, M. J. Australia **1**:717-723 (June 14) 1941.

55. Veasey, C. A., Jr.: Vitamins of the B Group and Their Relation to Ophthalmology, Tr. Am. Ophth. Soc. **38**:538-579, 1940. Jones, I. H.: Vitamins and the Eye, Ear, Nose and Throat, Laryngoscope **51**:609-682 (July) 1941.

56. Jolliffe, N.: Newer Knowledge of the Vitamin B-Complex, Bull. New York Acad. Med. **17**:195-204 (March) 1941.

57. Bueding, E.; Stein, M. H., and Wortis, H.: Blood Pyruvate Curves Following Glucose Ingestion in Normal and Thiamine-Deficient Subjects, J. Biol. Chem. **140**:697-703 (Sept.) 1941.

58. Shils, M. E.; Day, H. G., and McCollum, E. V.: The Urinary Excretion of Bisulfite Binding Substances by Human Adults on Thiamine-Low Diets, Am. J. M. Sc. **201**:561-569 (April) 1941.

59. Williams, R. D.; Mason, H. L.; Wilder, R. M., and Smith, B. F.: Observations on Induced Thiamine (Vitamin B_1) Deficiency in Man, Arch. Int. Med. **66**:785-799 (Oct.) 1940.

60. Williams, R. D., and Mason, H. L.: Further Observations on Induced Thiamine (Vitamin B_1) Deficiency and Thiamine Requirement of Man: Preliminary Report, Proc. Staff Meet., Mayo Clin. **16**:433-438 (July 9) 1941.

observed elevated values for blood pyruvic acid irregularly. In addition to disturbance of metabolism, the conspicuous manifestations of deficiency of thiamine were gross changes of behavior and other objective evidence of psychic disturbances involving mental depression, irritability and loss of efficiency.

Using a special method for micromeasurement of pyruvic acid in the blood of rats, Li and Kato [61] reported that by the end of the first month of thiamine depletion the amount of pyruvate in the blood increased more than 260 per cent over normal basal amounts and that during the second month it increased almost 500 per cent. It was observed that the quantity of pyruvate in the blood appeared to correspond roughly to the severity of the clinical manifestations. On the injection of thiamine into these polyneuritic animals there was a marked decrease in the content of pyruvate in the blood. If after the injection of thiamine this characteristic decrease in blood pyruvate did not occur the animal died within twenty-four hours. In a similar study [62] it has been shown that there is a rapid increase in the bisulfite-binding substances in the urine of rats subsisting on a vitamin B_1–deficient diet. The administration of thiamine brings the values for bisulfite-binding substances to normal within twenty-four hours. It is assumed that the rapid response to the administration of thiamine indicates that vitamin deficiency is responsible for the elevated values. It has also been pointed out [63] that the ingestion of a high fat diet will reduce the excretion of bisulfite-binding substances in the urine of rats deficient in thiamine.

Using a chemical method for measurement of the concentration of pyruvic acid in the blood, Kato and Li [64] reported that of a total of one hundred and fifty determinations made of the concentration of pyruvate in the blood of infants and children of all ages suffering from diverse diseases and conditions, the values in approximately 27 per cent were abnormally high, indicating that relative states of thiamine deficiency were present.

Apparently, a long-continued subminimal intake of thiamine hydrochloride produces a rather definite syndrome in dogs. Street and his

61. Li, P. K., and Kato, K.: Determination of Blood Pyruvate in Vitamin B_1 Deficiency, J. Lab. & Clin. Med. **26**:1314-1321 (May) 1941.

62. Shils, M. E.; Day, H. G., and McCollum, E. V.: The Effect of Thiamine Deficiency in Rats on the Excretion of Pyruvic Acid and Bisulfite-Binding Substances in the Urine, J. Biol. Chem. **139**:145-161 (May) 1941.

63. Banerji, G. G.: Effect of a High-Fat Diet on the Excretion of Bisulphite-Binding Substances in the Urine of Rats Deficient in Vitamin B_1, Biochem. J. **34**:1329-1333 (Sept.) 1940.

64. Kato, K., and Li, P. K.: Quantitative Determination of the Pyruvic Acid Content of the Blood in Infants and in Children: An Attempt to Diagnose Subclinical Deficiency of Vitamin B_1, Am. J. Dis. Child. **61**:1222-1237 (June) 1941.

associates [65] studied dogs in which the store of thiamine had been depleted. These dogs were maintained in a state of subnutrition for seventy-six to two hundred and ninety-three days, receiving a diet containing thiamine only in amounts averaging about 2 micrograms per kilogram of body weight daily. In these animals there developed a condition characterized by moderate spasticity of the hindlegs, unsteadiness, staggering and vomiting. In 2 animals, after three hundred and forty-five and three hundred and fifty-four days, respectively, of this insufficient intake of thiamine, the administration of large doses of thiamine hydrochloride for a month failed to have an appreciable effect on the syndrome. Histologic studies of the nervous system of representative animals revealed extensive myelin degeneration both of the peripheral nerves and of the posterior column of the spinal cord. Other workers [66] have observed definite symptoms of cardiac failure among dogs subsisting on diets deficient in thiamine.

Since vitamins serve as catalysts in the various phases of cellular combustion, the requirements in intake of them undoubtedly vary as the combustion rate increases or decreases with changes in environmental temperature. An interesting but so far unconfirmed observation by Mills [67] was that the optimal requirements of thiamine per gram of food were twice as high at a temperature of 91 F. as they were at a temperature of 65 F. and that an intake of thiamine higher than that required for a temperature of 91 F. served to protect against the depressant effects of even more excessive heat. Mills observed that among young rats subsisting on a diet thoroughly adequate in every way except for thiamine content, signs of inadequacy (lowered consumption of food and retarded growth) developed in animals in the hot room at dietary thiamine values which were entirely adequate for animals in the cold room. Protection against the severe effects of excessive heat is afforded by an accessory intake of thiamine in excess of the ordinary daily need. Mills brought out the fact that the need for a higher content of thiamine in food in tropical warmth or in the summer heat of the temperate zone has certain important bearings on the problems of human existence. He stated that protein foods in general have a high content of thiamine, but that people tend to avoid them in the presence of tropical warmth because of their greater specific dynamic action and higher cost.

65. Street, H. R.; Zimmerman, H. M.; Cowgill, G. R.; Hoff, H. E., and Fox, J. C., Jr.: Some Effects Produced by Long-Continued Subminimal Intakes of Vitamin B_1, Yale J. Biol. & Med. **13**:293-308 (Jan.) 1941.

66. Swank, R. L.; Porter, R. R., and Yeomans, A.: The Production and Study of Cardiac Failure in Thiamine-Deficient Dogs, Am. Heart J. **22**:154-168 (Aug.) 1941.

67. Mills, C. A.: Environmental Temperatures and Thiamine Requirements, Am. J. Physiol. **133**:525-531 (July) 1941.

Drill,[68] in experimental studies on dogs, reported that anorexia is not a primary effect of hyperthyroidism in animals with this disease but is a secondary symptom referable to deficiency of thiamine. Many other interesting physiologic effects of thiamine also have been reported.[69]

Methods of Measuring Vitamin B_1.—There continues to be considerable interest in this field. Several new methods for the measurement of thiamine in metabolic excretions, in the blood and in cereal products have been described.[70]

Cahill [71] reported that alterations of the fat-carbohydrate ratio of the diet of adult human beings have no significant effect on the urinary excretion of thiamine. He interpreted his observations to mean that in tests involving study of the excretion of thiamine in the urine no concern need be given to the fat-carbohydrate ratio of the foods eaten by the patients just prior to the time of determination.

Benson, Witzberger and Slobody [72] reported that the urinary excretion of thiamine among normal children ranges between 92 and 602 micrograms (of thiamine hydrochloride) per day and averages 268 micrograms per day. Their study was made on children between 7 and

68. Drill, V. A.: The Calorie Intake and Weight Balance of Hyperthyroid Dogs in Relation to Vitamin B_1 and Yeast, Am. J. Physiol. **132**:629-635 (April) 1941.

69. Guerrant, M. V., and Dutcher, R. A.: The Influence of Exercise on the Growing Rat in the Presence and Absence of Vitamin B_1, J. Nutrition **20**:589-598 (Dec.) 1940. Barnes, R. H., and MacKay, E. M.: Influence of Protamine Zinc Insulin upon Appetite During Anorexia of Vitamin B_1 Deficiency, Proc. Soc. Exper. Biol. & Med. **45**:759-762 (Dec.) 1940. Smith, A. H., and Meyer, C. E.: The Influence of Thiamine Deficiency on Citric Acid Excretion, J. Biol. Chem. **139**:227-231 (May) 1941. Govier, W. M., and Greer, C. M.: Studies on Shock Induced by Hemorrhage: I. Effect of Thiamine on Survival Time, J. Pharmacol. & Exper. Therap. **72**:317-320 (Aug.) 1941. Flexner, J.; Bruger, M., and Wright, I. S.: Experimental Atherosclerosis: II. Effect of Thiamine Hydrochloride and Ascorbic Acid on Experimental Atherosclerosis in Rabbits, Arch. Path. **31**:82-84 (Jan.) 1941.

70. Jowett, M.: The Estimation of Vitamin B_1 in Urine, Biochem. J. **34**:1348-1355 (Nov.) 1940. Slater, E. C.: The Thiochrome Method of Estimating Thiamine (Vitamin B_1) in Urine, Milk and Cereal Products, Australian J. Exper. Biol. & M. Sc. **19**:29-32 (March) 1940. Schultz, A. S.; Atkin, L., and Frey, C. N.: A Method for the Determination of Thiamine and Certain of Its Metabolic Products in Urine, J. Biol. Chem. **136**:713-717 (Dec.) 1940. Hennessy, D. J.: Chemical Methods for the Determination of Vitamin B_1, Indust. & Engin. Chem. (Analyt. Ed.) **13**:216-218 (April 15) 1941. Pollack, H.; Ellenberg, M., and Dolger, H.: Clinical Studies on Vitamin B_1 Excretion Determined by the Fermentation Method, Arch. Int. Med. **67**:793-804 (April) 1941.

71. Cahill, W. M.: Urinary Excretion of Thiamine on High Fat and High Carbohydrate Diets, J. Nutrition **21**:411-418 (April) 1941.

72. Benson, R. A.; Witzberger, M., and Slobody, L. B.: The Urinary Excretion of Thiamine in Normal Children, J. Pediat. **18**:617-620 (May) 1941.

10 years old. Using the method for measurement of thiamine described by Hennessy and Cerecedo, Najjar and Holt [73] found that the daily excretion of thiamine by 23 normal adult persons varied between the wide limits of 60 and 342 micrograms (of thiamine hydrochloride) a day. These observations are in agreement with those of many other workers. The authors found that the daily excretion of thiamine by children is comparable to that of adult persons, but a patient who had hyperthyroidism also had a low rate for excretion of thiamine, as was noted among other patients suffering from a definite vitamin B deficiency syndrome. The authors found that persons subsisting on a diet deficient in thiamine who are symptom free may excrete less thiamine than patients who have frank beriberi. Therefore they expressed the belief that if progress is to be made, it will be necessary to search for more sensitive tests, with results dependent on the immediate intake. It was also observed that their thiamine excretion test (intravenous injection of 1 mg. of thiamine hydrochloride and check of the urine for four hours thereafter) was a more reliable index of the bodily stores of thiamine than was the customary measurement of the total twenty-four hour output of thiamine in the urine, but it was difficult even by means of this excretion test to distinguish thiamine deficiency from thiamine subnutrition.

However, Williams and Mason,[60] who maintained human subjects on a constant diet for one hundred and forty days and gave thiamine hydrochloride in gradually increasing doses, found that the excretion of thiamine closely reflected the state of thiamine nutrition. The urinary excretion clearly distinguished between restriction of intake just prior to the test and prolonged, moderate restriction of this vitamin. The variations in the excretion of thiamine among so-called normal persons possibly represent, at least in part, variations in states of thiamine nutrition encountered in the population at large. In Najjar and Holt's [73] series, values for thiamine in the blood serum of several normal adult persons ranged, as a rule, between 1 and 3 micrograms (of thiamine hydrochloride) per hundred cubic centimeters. From some subjects they were unable to recover measurable quantities of thiamine. This led them to conclude that the value for thiamine in the serum alone does not constitute a satisfactory criterion for measurement of thiamine deficiency and that probably, like the value for the twenty-four hour excretion in the urine, it is dependent on the immediate intake of thiamine. Carden, Province and Ferrebee [74] also have pointed out that much more study is

73. Najjar, V. A., and Holt, L. E.: Studies in Thiamine Excretion, Bull. Johns Hopkins Hosp. **67**:107-124 (Aug.) 1940.

74. Carden, G. A.; Province, W. D., and Ferrebee, J. W.: Clinical Experiences with the Measurement of the Urinary Excretion of Vitamin B_1, Proc. Soc. Exper. Biol. & Med. **45**:1-5 (Oct.) 1940.

needed, for better understanding of the factors related to the saturation and urinary excretion of thiamine, before accurate interpretation of these results can be made. In one year these investigators were unable to find any patient whose urinary excretion of vitamin B_1 could not be increased to normal by the administration of small amounts of vitamins, amounts comparable to those obtained in an ordinary diet.

Requirements of the Normal Person.—Melnick, Robinson and Field [75] have shown that thiamine is stable during a sixteen hour incubation period at 37.5 C. in gastric juice with a p_H of 1.5 to 8 obtained from normal subjects. In the presence of an antacid, thiamine added to gastric juice may be absorbed or destroyed during this period of incubation. Thiamine was found to be stable in hemin-containing gastric juice and in gastric juice obtained from patients who had achlorhydria. On the other hand, when thiamine is incubated for sixteen hours with bile at its natural p_H there is an apparent loss of 50 to 90 per cent of the vitamin. As the reaction of the bile becomes acid, less thiamine is destroyed, and complete recovery can be obtained from samples incubated at a p_H of 4.5. Results obtained when thiamine is incubated with pancreatic juice are similar to those obtained when it is incubated with bile. It should be mentioned that all these experiments were conducted in vitro, an important factor, in that thiamine is more stable in its natural environment than it is in pure aqueous solution. The authors expressed the belief that the losses in vivo probably are appreciably less than those they noted in vitro, because of the protective action of the other constituents of the diet.

Stockholm, Althausen and Borson [76] recently reported that thiamine probably is absorbed in the intestine by means of simple diffusion and that absorption is roughly proportional to the concentration of thiamine in the intestine. These authors also concluded that phosphorylation did not play a dominant part in the rate of intestinal absorption of thiamine.

Little had been added to previous studies concerning the normal human requirements of thiamine before the report published recently by Williams and Mason.[60] These investigators found that 0.22 to 0.25 mg. of thiamine for each thousand calories of a mixed diet was not enough for 11 women, for in all of them signs and symptoms of deficiency developed when this amount of thiamine was provided. In a study of thiamine requirements they found that the optimal intake of thiamine for the subjects of their study was not less than 0.5 mg. and not more than 1.0 mg. per thousand calories obtained from a diet of ordinary composition.

75. Melnick, D.; Robinson, W. D., and Field, H., Jr.: Fate of Thiamine in the Digestive Secretions, J. Biol. Chem. **138**:49-61 (March) 1941.

76. Stockholm, M.; Althausen, T. L., and Borson, H. J.: Mechanism of Intestinal Absorption of Thiamine, Proc. Soc. Exper. Biol. & Med. **46**:387-390 (March) 1941.

Knott,[77] in a study of 12 infants 1 to 6 months old, substantiated previous conclusions, based on tests for urinary excretion, that 80 international units of thiamine daily represents the minimal requirements for infants in this age range. Other authors [78] observed that in the age group of 7 to 10 years 45 micrograms of thiamine per hundred calories, or 990 micrograms, daily seems to be adequate to maintain excellent health. The average amount of thiamine excreted by children of this age was found to be about 27 per cent of the intake.

In a study of a small number of healthy Javanese, Meyers [79] observed that the output of thiamine was considerably lower than the average found in the more temperate parts of the world. This author suggested the possibility that some sort of adaptation to a low intake of vitamin B_1 occurs among these persons. He pointed out that a low level of thiamine in the body stores should not without additional evidence be held to be associated directly with a deficiency syndrome. Undoubtedly, the intake of thiamine among the Javanese under consideration is much lower than the average intake in other parts of the world; it probably is, on the average, a level which might produce clinical symptoms among Caucasians under experimental conditions. Meyers' study suggested that a low intake of thiamine can continue for years without the production of gross clinical evidence of deficiency and that some degree of adaptation is possible.

Apparently there is a smaller amount of thiamine in evaporated milk than in whole milk.[80] Although 6 per cent of the thiamine in whole milk is present in a free state, the rest is combined in a nondialyzable form, probably being combined with protein.[81] Investigation of the effects of long cooking of cereals on the stability of thiamine [82] reveals that no significant loss occurs, whereas in the presence of alkali, such as in the cooking of baking powder muffins, the loss of thiamine may amount to as much as 50 per cent.[83]

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77. Knott, E. M.: Determination of Vitamin B_1 Requirement of Infants by Means of Urinary Excretion of Thiamine, Proc. Soc. Exper. Biol. & Med. **45**:765-766 (Dec.) 1940.

78. Benson, R. A.; Witzberger, C. M., and Slobody, L. B.: The Urinary Excretion of Thiamine in Normal Children, J. Pediat. **18**:617-620 (May) 1941.

79. Meyers, F. M.: Possible Adaptation to a Low Vitamin B_1 Intake, Am. J. M. Sc. **201**:785-789 (June) 1941.

80. Daniels, A. L.: Further Evidence of Destruction of Thiamine in Evaporated Milk, Am. J. Dis. Child. **62**:127-129 (July) 1941.

81. Halliday, N., and Deuel, H. J., Jr.: The Presence of Free and Combined Thiamine in Milk, J. Biol. Chem. **140**:555-561 (Aug.) 1941.

82. Hanning, F.: The Effect of Long Cooking upon the Stability of Thiamine (Vitamin B_1) in Cereals, J. Am. Dietet. A. **17**:527-530 (June-July) 1941.

83. Fincke, M. L., and Little, R. R.: The Thiamine (Vitamin B_1) Values of Wheat Germ Muffins, J. Am. Dietet. A. **17**:531-534 (June-July) 1941.

Clinical Deficiencies of Thiamine.—It seems fairly well established that a syndrome resembling neurasthenia can be produced by a diet deficient in thiamine. This problem is complicated by the fact that similar syndromes have been reported to be cured by nicotinic acid, pyridoxine and vitamin E. In an excellent discussion of this problem, Wortis and Jolliffe [84] reemphasized the fact that the clinical picture of this syndrome is extremely varied, that many similar pictures occur among apparently well nourished persons and that these symptoms frequently can be abated by psychotherapy as well as by vitamin therapy. Therefore, it should not be inferred that neurasthenia in every case is based on thiamine deficiency or other nutritional deficiencies, although it does seem fairly certain that a syndrome presenting many of the characteristics of the ill defined neurasthenic syndrome can be produced by nutritional deficiencies.

Investigation of the effect of thiamine in the treatment of various neurologic disturbances continues. The exact relation of thiamine to the metabolism of nerve tissue, however, is still incompletely understood.

Zillhardt, MacLean and Murphy [85] reported the results of a rather extensive study which suggest that the administration of thiamine hydrochloride may have a beneficial effect on those neural signs and symptoms of pernicious anemia that seem to be stationary in spite of persistent intensive anti-pernicious-anemia therapy. The authors pointed out that the beneficial effects occur during the first two months of treatment and that apparently the continued use of thiamine after this period does not produce any further changes. Again, the authors stressed the many variables involved in the attempt to quantitate neurologic symptoms and signs in such a clinical study.

Rapid relief of pain caused by herpes zoster of the trunk has been reported [86] to follow the intracutaneous and subcutaneous injection of 10 mg. of thiamine hydrochloride into a clear portion of skin between the anterior and the lateral patches of eruption. The effect was noted a few hours later, when the pain practically disappeared. To be of clinical value, this type of report requires a much larger series of cases than that which thus far has been reported.

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84. Wortis, H., and Jolliffe, N.: The Present Status of Vitamins in Nervous Health and Disease, New York State J. Med. **41**:1461-1470 (July 15) 1941.

85. Zillhardt, J. C.; MacLean, K., and Murphy, W. P.: The Effect of Thiamine on the Residual Neural Disturbances of Treated Pernicious Anemia, Ann. Int. Med. **15**:33-43 (July) 1941.

86. Smith, S. F.: Regional Injection of Thiamine Chloride in Herpes Zoster, J. M. Soc. New Jersey **38**:396-397 (Aug.) 1941.

In a well controlled study Rose and Jacobson [87] showed that thiamine hydrochloride has no specific beneficial effect in the treatment of trigeminal neuralgia.

In last year's review it was reported that among animals abstinence symptoms in addiction to morphine were markedly decreased after the administration of thiamine hydrochloride. In a well controlled study of morphine addiction in man, Himmelsbach [88] reported that the administration of thiamine prior to and after withdrawal of morphine had no demonstrable effect on the onset of the abstinence symptoms; likewise, the administration of thiamine during the course of addiction had no demonstrable effect on the patient. Similarly, it was stressed in last year's review that thiamine deficiency was the cause of delirium tremens. Wortis and Jolliffe [84] have not been able to confirm these observations. They did assert, however, that delirium tremens is a factor of considerable importance in the production of other nutritional disturbances of the nervous system (Wernicke's syndrome, deficiency of nicotinic acid, encephalopathy, peripheral neuropathy). For this reason, Wortis and Jolliffe expressed the belief that thiamine and nicotinic acid, as well as the entire vitamin B complex, should be administered to all patients who have delirium so that the development of peripheral neuropathy can be prevented. Wortis and Jolliffe [84] have reported clinical observations made in 27 cases of Wernicke's syndrome. They pointed out that this syndrome originally was described by Wernicke as probably constituting a combination of several nutritional deficiencies affecting the nervous system, one of which is deficiency of thiamine. Green, Carlson and Evans [89] recently have reported that a deficiency disease of foxes produced by the feeding of fish is analogous to Wernicke's disease in man. These authors assumed that this deficiency in foxes is a thiamine deficiency.

Considerable controversy continues to be apparent concerning the effect of thiamine hydrochloride on diabetes mellitus. It has been pointed out on several occasions that the administration of thiamine hydrochloride has no effect on the blood sugar of diabetic persons or on that of normal persons, nor does the intravenous injection of thiamine hydrochloride have any effect on the dextrose tolerance curve of diabetic and of non-

87. Rose, A. S., and Jacobson, B. M.: Treatment of Trigeminal Neuralgia with Vitamin B_1 (Thiamine Hydrochloride), Arch. Neurol. & Psychiat. **44**:1307-1311 (Dec.) 1940.

88. Himmelsbach, C. K.: Thiamine in the Treatment of the Morphine Abstinence Syndrome in Man, J. Pharmacol. & Exper. Therap. **70**:293-296 (Nov.) 1940.

89. Green, R. G.; Carlson, W. E., and Evans, C. A.: A Deficiency Disease of Foxes Produced by Feeding Fish: B_1 Avitaminosis Analogous to Wernicke's Disease of Man, J. Nutrition **21**:243-256 (March) 1941.

diabetic persons.[90] In a study of 422 ambulant diabetic patients, Fein, Ralli and Jolliffe [91] observed that 9, or 2.1 per cent, had a symmetric type of peripheral neuropathy which was characteristic of peripheral neuropathy among persons having true vitamin B_1 deficiency. The daily oral administration of 10 mg. of thiamine hydrochloride without other changes in the regimen resulted in the cure of 8 subjects and improvement for the ninth. These authors concluded that the symmetric type of peripheral neuropathy, beginning first in, and involving primarily, the lower extremities of patients suffering from diabetes mellitus can be abated by the administration of thiamine hydrochloride. In their opinion, the condition is due to deficiency of vitamin B_1. They, like others, reported inconsistent results in the treatment of single nerves or the vague aches and pains of diabetic patients.

Wallace [92] reported that the parenteral administration of thiamine hydrochloride and ascorbic acid concurrently with irradiation prevented the appearance of many of the general symptoms of irradiation sickness. It was found that nausea and vomiting were entirely eliminated. It is believed generally that thiamine is of value in the treatment of almost any disease in which chronic diarrhea occurs. It has been reported,[93] however, that it is of no value in the treatment of chronic ulcerative colitis. Veasey [94] discussed the use of vitamin B complex in the treatment of ophthalmic conditions. Cases in which beriberi heart resulting from deficiency of thiamine is cured after the administration of thiamine continue to be reported.[95]

In an interesting paper Laws [96] described a case of sensitization to thiamine hydrochloride. The patient (a woman) apparently was not

90. Kaufman, R. E.: Influence of Thiamine on Blood Sugar Levels in Diabetic Patients, Arch. Int. Med. **66**:1079-1086 (Nov.) 1940. Wassmann, K.: Vitamin B_1 and Blood Sugar, Acta med. Scandinav. **106**:159-167, 1941. Trasoff, A., and Bordin, C.: The Use of Vitamin B_1 in Diabetes Mellitus: A Clinical Study, Am. J. Digest. Dis. **8**:1-2 (Jan.) 1941.

91. Fein, H. D.; Ralli, E. P., and Jolliffe, N.: Peripheral Neuropathy Due to Vitamin B_1 Deficiency in Diabetes Mellitus, J. A. M. A. **115**:1973-1976 (Dec. 7) 1940.

92. Wallace, W. S.: Studies in Radiation Sickness: II. Vitamins B_1 and C and the Small Intestinal Change in Radiation Sickness, South. M. J. **34**:170-173 (Feb.) 1941.

93. Shiffer, P., and Ferguson, L. K.: The Treatment of Idiopathic Ulcerative Colitis with Concentrated Liver Extract and Vitamin B_1, Am. J. Digest. Dis. **8**:300-301 (Aug.) 1941.

94. Veasey, C. A., Jr.: Vitamin B in Ophthalmology, Arch. Ophth. **25**:450-468 (March) 1941.

95. Konstam, G., and Sinclair, H. M.: Cardiovascular Disturbances Caused by Deficiency of Vitamin B_1, Brit. Heart J. **2**:231-240 (Oct.) 1940. Swan, W. G. A., and Laws, F.: A Case of Beri-Beri Heart, ibid. **2**:241-246 (Oct.) 1940.

96. Laws, C. L.: Sensitization to Thiamine Hydrochloride, J. A. M. A. **117**: 176 (July 19) 1941.

sensitive to thiamine at the beginning of treatment, but after several injections she became so. About thirty minutes after one treatment her eyes and lips became edematous, large urticarial wheals appeared over the body and a feeling of tightness was experienced in the thorax; she became dyspneic and cyanotic and wheezed audibly. Epinephrine was administered within a few minutes, and at the end of five or six hours the entire reaction had subsided. Intradermal tests conducted with the commercial preparation of thiamine hydrochloride which had been used throughout the course of these injections produced a large urticarial wheal. Passive transfer was made to a nonallergic person, and at the end of forty-eight hours the sensitized sites reacted strongly when the same preparation of thiamine was introduced. A solution of thiamine hydrochloride prepared in water without the addition of other substance produced exactly the same type of reaction as did the commercial preparation, in which there was a preservative. This author suggested that it would be advisable to make intradermal tests with thiamine hydrochloride before administering it parenterally, particularly to patients who have received thiamine previously. Stiles [97] also pointed out that if it is desired to use intradermal tests for the detection of patients who have become hypersensitive to thiamine hydrochloride, more dilute preparations containing probably not more than 5 mg. per cubic centimeter should be used.

NICOTINIC ACID

Chemical and Physiologic Properties.—It has been known for some time that the cozymase content of animal tissues closely parallels the state of nicotinic acid nutrition, and there is no reason to believe that the same state of affairs does not exist among human beings. Whereas the administration of nicotinic acid has been shown invariably to raise the level of the factor V in human blood, the fact remains that these substances are not uniformly diminished in the blood of pellagrins. Axelrod, Spies and Elvehjem [98] recently showed that deficiency of nicotinic acid produced a marked diminution of coenzyme I in the striated muscle of human subjects, although only a slight effect was noted in the content of the erythrocytes in the blood of the same persons. Evaluation of the physiologic significance of this observation awaits the uncovering of additional knowledge concerning the quantitative relation between the coenzyme I content of human muscle and the ability of the muscle to carry out its oxidative functions. A decrease in the

97. Stiles, M. H.: Hypersensitivity to Thiamine, J. A. M. A. **117**:954 (Sept. 13) 1941; Hypersensitivity to Thiamine Chloride with a Note on Sensitivity to Pyridoxine Hydrochloride, J. Allergy **12**:507-509 (July) 1941.

98. Axelrod, A. E.; Spies, T. D., and Elvehjem, C. A.: The Effect of a Nicotinic Acid Deficiency upon the Coenzyme I Content of the Human Erythrocyte and Muscle, J. Biol. Chem. **138**:667-676 (April) 1941.

value for factor V in dog muscle, however, produces changes in its oxidative metabolism, and it may be expected that a similar relation is operative in human muscle. Although the importance of these observations cannot be overestimated, the authors advanced new problems in the same investigation by their observation that the antipellagra value of a compound does not necessarily parallel its ability to increase the coenzyme content of the tissues. Whereas the effect of nicotinic acid is marked in both respects, pyrazine monocarboxylic acid and pyridine betacarboxylic acid diethylamide (coramine) produced no consistent increase in values for coenzyme, despite clinical improvement among pellagrins. This agrees with the results of Dann and his co-workers,[99] who were unable to increase the content of the V factor in human blood by the administration of quinolinic acid and the pyrazine acids. These same substances failed to exhibit antiblacktongue activity in dogs, and these workers were inclined to doubt the antipellagra activity of the compounds. It is obvious, on the basis of these two papers alone, that there is still much to be learned about the pathologic physiology of pellagra.

Although the past year has been productive of much effort in such a direction, there is as yet no satisfactory laboratory procedure for the diagnosis of pellagra. Field and associates[100] presented an excellent review of this subject; they found estimates of the normal content of nicotinic acid in the blood to vary from 0.25 to 0.89 mg. per hundred cubic centimeters of whole blood. Values reported during the past year[101] are not in much better agreement than these figures. Much of this discrepancy is due to the use of different methods and to the fact that the chemical methods now in use are not specific for the detection of nicotinic acid. It is generally agreed that the major portion of the

99. Dann, W. J.; Kohn, H. I., and Handler, P.: The Effect of Pyrazine Acids and Quinolinic Acid on the V-Factor Content of Human Blood and upon Canine Blacktongue, J. Nutrition **20**:477-490 (Nov.) 1940.

100. Field, H., Jr.; Melnick, D.; Robinson, W. D., and Wilkinson, C. F., Jr.: Studies on the Chemical Diagnosis of Pellagra (Nicotinic Acid Deficiency), J. Clin. Investigation **20**:379-386 (July) 1941.

101. (*a*) Kochhar, B. D.: The Quantitative Estimation of Nicotinic Acid in Blood and Other Body Fluids, Indian J. M. Research **28**:385-396 (Oct.) 1940; (*b*) Nicotinic Acid in Blood, ibid. **29**:133-136 (Jan.) 1941; (*c*) Nicotinic Acid in Blood and in Urine, ibid. **29**:341-350 (April) 1941. (*d*) Perlzweig, W. A.; Levy, E. D., and Sarett, H. P.: Nicotinic Acid Derivatives in Human Urine and Their Determination, J. Biol. Chem. **136**:729-745 (Dec.) 1940. (*e*) Briggs, A. P.: Excretion of Nicotinic Acid in Pellagra, Proc. Soc. Exper. Biol. & Med. **46**:374-378 (March) 1941. (*f*) Bandier, E.: The Nicotinic Acid Content of Blood and Urine, Acta med. Scandinav. **107**:62-79, 1941. (*g*) Isbell, H.; Wooley, J. G.; Butler, R. E., and Sebrell, W. H.: A Bacterial Assay Method for Nicotinamide and Related Substances in Blood, Urine, and Spinal Fluid, J. Biol. Chem. **139**:499-510 (June) 1941.

nicotinic acid is found in the erythrocytes and that determinations must be carried out on samples of whole blood.[102] Although normal values for nicotinic acid have varied widely in different reports, it is highly significant that there has been no important difference in these values reported for normal persons and those reported for pellagrins. Field and his associates [100] found a rather pronounced and consistent decrease in the urinary excretion of trigonelline (the form in which the greater part of nicotinic acid is excreted) among persons deficient in nicotinic acid, and they expressed the opinion that this observation may prove to be of value in the future. Kochhar [101c] and Perlzweig, Levy and Sarett [101d] conducted experiments on the excretion of nicotinic acid in the urine of human beings after the administration of test doses, but the value of this work cannot be assessed, since they used only normal persons. Kark and Meiklejohn [103] have produced additional evidence against porphyrinuria as a diagnostic adjunct in pellagra. They concluded on the basis of study of several cases that its appearance is coincidental and is dependent on hepatic dysfunction rather than on any essential part of pellagra.

Several articles in which new methods for the determination of nicotinic acid and its derivatives were explained appeared in the last year.[104] For those persons interested in the chemistry of nicotinic acid [105] we have listed two excellent reviews on this subject.

Mainzer and Krause [106] made the interesting observation that pellagrins, like patients suffering from Addison's disease, are hypersensitive to insulin and that prolonged and marked hypoglycemia occurs when they receive doses (5 units) which are otherwise ineffective. Among persons who had chronic pellagra this phenomenon persisted after cure

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102. Field, Melnick, Robinson and Wilkinson.[100] Footnotes 101 *a* and *f*.

103. Kark, R., and Meiklejohn, A. P.: Pellegra and Porphyrinuria, Am. J. M. Sc. **201**:380-385 (March) 1941.

104. Giri, K. V., and Naganna, B.: An Adsorption Method for the Estimation of Nicotinic Acid Content of Foodstuffs, Indian J. M. Research **29**:125-132 (Jan.) 1941. Stotz, E.: A Clinical Method of the Determination of Nicotinic Acid in Blood and Urine, J. Lab. & Clin. Med. **26**:1042-1046 (March) 1941. Swaminathan, M.: Further Studies on the Cyanogen Bromide Method of Estimating Nicotinic Acid in Biological Materials, Indian J. M. Research **29**:325-340 (April) 1941. Dann, W. J., and Handler, P.: The Quantitative Estimation of Nicotinic Acid in Animal Tissues, J. Biol. Chem. **140**:201-213 (July) 1941. Noll, C. I., and Jensen, O. G.: The Chemical Determination of Nicotinic Acid in Milk and Milk Derivatives, ibid. **140**:755-762 (Sept.) 1941.

105. Bacharach, A. L.: The Distribution of Nicotinic Acid in Human and Animal Foods, Nutrition Abstr. & Rev. **10**:459-465 (Jan.) 1941. Waisman, H. A., and Elvehjem, C. A.: Chemical Estimation of Nicotinic Acid and Vitamin B_6, Indust. & Engin. Chem. (Analyt. Ed.) **13**:221-225 (April 15) 1941.

106. Mainzer, F., and Krause, M.: On Irreversible Functional Disturbances in Chronic Pellagra, Acta med. Scandinav. **104**:321-336, 1940.

or improvement, whereas among those who had acute pellagra cure was followed by restoration to normal of the response of the content of sugar in the blood to insulin. They concluded that qualitatively insufficient nutrition in some way produces irreversible injury to the homeostatic factors governing the content of sugar in the blood.

Petri and his associates [107] were able to produce pellagra in gastrectomized pigs, although the pigs had been fed a diet similar to that of hogs not operated on in which signs of deficiency did not develop. Neither nicotinic acid nor any other member of the vitamin B complex was effective in reversing the course of this type of pellagra in gastrectomized pigs or in arresting degeneration of nerve cells. The authors expressed the belief that this type of pellagra resembles the endogenous pellagra of man and concluded that the gastrectomized animals were unable to synthesize coenzymes from the available nicotinic acid.

Although others [108] have found nicotinic acid to be effective in reducing the clotting time of blood of patients who have febrile disease, Aggeler and Lucia [109] could not demonstrate a coagulant effect when this acid was tested in vitro with heparinized recalcified plasma. They observed that nicotinic acid is an active hemolytic agent and suggested that its coagulant effect is dependent on the release of thromboplastin from the disrupted elements of the blood, since nonhemolytic compounds of nicotinic acid were quite ineffective in promoting the coagulation of blood.

Clinical Use.—We feel that any review of the literature on nicotinic acid would be incomplete without mention of several excellent and complete summaries of the subject which will serve to bring the reader up to date,[110] although they are not strictly contributions in that they

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107. Petri, S.; Nørgaard, F., and Bandier, E.: Studies on the Causation of Experimental Gastroprival Pellagra: Therapeutic Experiment (Ib) with Preventive Peroral and Parenteral Administration of Nicotinic Acid, Acta med. Scandinav. **103**:584-606, 1940; Studies on the Causation of Experimental Gastroprival Pellagra: Therapeutic Experiment (II) with Preventive Parenteral Administration of Vitamin B_1, Riboflavin and Vitamin A, Separately and in the Combination Vitamin B_1 + Vitamin A, ibid. **104**:245-260, 1940.

108. Calder, R. M., and Kerby, G. P.: The Effect of Nicotinic Acid on Blood Coagulation, Am. J. M. Sc. **200**:590-596 (Nov.) 1940.

109. Aggeler, P. M., and Lucia, S. P.: Action of Nicotinic Acid on Coagulation of the Blood, Proc. Soc. Exper. Biol. & Med. **47**:522-525 (June) 1941.

110. Sydenstricker, V. P.: The Clinical Manifestations of Nicotinic Acid and Riboflavin Deficiency (Pellagra), Ann. Int. Med. **14**:1499-1517 (March) 1941; The Present Status of Nicotinic Acid, Arch. Int. Med. **67**:746-754 (April) 1941. Jolliffe, N.; Wortis, H., and Stein, M. H.: Vitamin Deficiencies and Liver Cirrhosis in Alcoholism: IV. The Wernicke Syndrome; V. Nicotinic Acid Deficiency Encephalopathy; VI. Encephalopathies with Possible Nutritional Involvement, Quart. J. Stud. on Alcohol **2**:73-97 (June) 1941.

do not offer anything new. In addition to these, Harris [111] has presented an exhaustive treatise on pellagra in his book "Clinical Pellagra."

Kooser and Blankenhorn [112] conducted an interesting survey among the residents of two adjacent communities in Kentucky, one mining and one rural, in both of which pellagra was once endemic. Persons of the two groups had been similar in economic status and food habits prior to a campaign of education in the health-sparing value of foods in the rural community. A study of the dietary habits of persons of the two groups revealed little difference in the consumption of pellagra-producing foods, but there was a significant increase in the pellagra-preventing foods eaten by members of the rural group. The result apparently was the complete eradication of pellagra in members of the rural group, whereas it was still endemic in the mining community, despite no change in economic status, at the time of the report by Kooser and Blankenhorn. The importance of this study cannot be overestimated from a public health standpoint.

Sydenstricker and Cleckley [113] presented data concerning 29 patients who had varying psychotic reactions, including lethargy, stupor, mania, hallucination and disorientation, all of whom exhibited a prompt response to nicotinic acid therapy. As the authors noted, the conditions of these patients do not fit into a single psychiatric classification but include that group "ordinarily diagnosed as toxic psychosis, exhaustion delirium, or perhaps, psychosis, type undetermined." Despite the complete lack of any evidence of pellagra, the response to the administration of nicotinic acid was remarkable in all cases, being usually prompt and often spectacular. The authors were led to express the belief that the psychotic symptoms manifested in these various disturbances have a basis in avitaminosis. In discussing this presentation, Aring made the interesting observation that the response of the patient to nicotinic acid possibly was referable not to the action of the acid as a vitamin but to its action as a vasodilator, with the resulting increased cerebral circulation. This suggestion is at variance, however, with the observations of Loman and his associates,[114] who administered nicotinic acid intravenously to human beings by way of the carotid and the brachial artery and reported the following results: 1. The pressure of the cerebrospinal fluid was insignificantly altered. 2. The caliber of the retinal vessels was unchanged.

111. Harris, S.: Clinical Pellagra, St. Louis, C. V. Mosby Company, 1941.

112. Kooser, J. H., and Blankenhorn, M. A.: Pellagra and the Public Health: A Dietary Survey of Kentucky Mountain Folk in Pellagrous and in Non-Pellagrous Communities, J. A. M. A. **116**:912-915 (March 8) 1941.

113. Sydenstricker, V. P., and Cleckley, H. M.: The Effect of Nicotinic Acid in Stupor, Lethargy and Various Other Psychiatric Disorders, Am. J. Psychiat. **98**:83-92 (July) 1941.

114. Loman, J.; Rinkel, M., and Myerson, A.: The Intracranial and Peripheral Vascular Effects of Nicotinic Acid, Am. J. M. Sc. **202**:211-216 (Aug.) 1941.

3. The cerebral blood flow, as determined by arteriovenous differences in oxygen content, was only slightly increased, whereas the flow to the arm was markedly increased. These same authors have suggested the possible usefulness of nicotinic acid in the treatment of Raynaud's disease, since it shortens the Raynaud-like response produced by epinephrine when both drugs are injected simultaneously into the brachial artery.

Smith and her associates [115] described a syndrome involving sebaceous glands which they found to be frequently associated with pellagra and which they have termed "dyssebacia." The lesions are found chiefly on the face and consist of plugs of inspissated sebum projecting from the sebaceous follicles, producing a "sandpaper" appearance. Microscopically, hyperplasia of the sebaceous glands, with dilatation and plugging of the follicles, is evident. Nicotinic acid was curative in most cases, although it was not so effective as yeast or crude extracts of liver.

RIBOFLAVIN

Chemical and Physiologic Properties.—Since the yellow enzyme, of which riboflavin is a constituent, is concerned in part with carbohydrate metabolism, it has long been felt that deficiency of this substance, like deficiency of thiamine, should result in some changes in the nervous system. It has been established that in acute riboflavin deficiency in dogs profound collapse occurs within one hundred to one hundred and fifty days after institution of the diet deficient in riboflavin and that this condition can be treated successfully by prompt administration of the missing factor. These animals do not exhibit specific neurologic disturbances. In a recent paper, however, Street and his associates [116] reported that long subsistence on a diet low in riboflavin leads to the development of neurologic abnormalities in dogs, as evidenced by clumsiness and, finally, by loss of the deep reflexes of the limbs. These symptoms are accompanied by myelin degeneration of the peripheral nerves and of the posterior columns of the spinal cord. These changes become more extensive as the period of subsistence on the deficient diet continues. Apparently, the levels of urea nitrogen, nonprotein nitrogen, uric acid and hemoglobin in the blood are not affected in the presence of riboflavin deficiency in dogs.[117] However, a decrease of 27 per cent in the values for riboflavin in the blood was found in dogs in acute

115. Smith, S. G.; Smith, D. T., and Callaway, J. L.: Dysfunction of the Sebaceous Glands Associated with Pellagra, J. Invest. Dermat. **4**:23-42 (Feb.) 1941.

116. Street, H. R.; Cowgill, G. R., and Zimmerman, H. M.: Further Observations of Riboflavin Deficiency in the Dog, J. Nutrition **22**:7-24 (July) 1941.

117. Axelrod, A. E.; Lipton, M. A., and Elvehjem, C. A.: Riboflavin Deficiency in the Dog, Am. J. Physiol. **133**:555-561 (July) 1941.

stages of deficiency, and the average daily urinary excretion of riboflavin by these animals was markedly reduced.

In contrast, deficiency of riboflavin in the pig is characterized clinically by retarded growth, corneal opacities, changes in the skin and hair and collapse, sometimes associated with hypoglycemia.[118] In an excellent paper by Patek and his associates, it was observed that 4 pigs subsisting on the basal diet collapsed in three, six, seven and ten months, respectively, after the experimental feeding was begun. The pigs suddenly became listless and refused to eat. The extremities became cold and cyanotic, and the animals were found in a state of collapse. Two of the animals were revived by the parenteral administration of riboflavin. One received 100 mg. intravenously three hours after the onset of collapse, and 1 received 200 mg. intravenously nearly two hours after the onset of collapse. The response to these injections was dramatic. The animals suddenly grunted, stood up, walked and ate their food. They were unsteady on their hindlegs for several days, however, after which the ataxia disappeared. Hypoglycemia was present throughout the collapse syndrome, but some data suggested that this syndrome was not the direct result of hypoglycemia. The authors pointed out that it is possible that deficiency of riboflavin interferes with the proper utilization of dextrose. It has also been reported [119] that riboflavin metabolism is intimately connected with fat metabolism in growing animals.

Apparently, riboflavin alone affords no significant protection against hepatic cancer caused by the administration of butter yellow (dimethylaminoazobenzene). When nicotinic acid was combined with riboflavin, however, a decrease of 50 per cent in the incidence of cancer resulted and when casein was administered as an additional supplement (to 200 micrograms of riboflavin given daily) the protective effect was striking, although not absolute.[120]

Several methods [121] have been employed for the determination of riboflavin. General discussion and comparison of these various methods

118. Patek, A. J., Jr.; Post, J., and Victor, J.: Riboflavin Deficiency in the Pig, Am. J. Physiol. **133**:47-55 (May) 1941.

119. Mannering, G. J.; Lipton, M. A., and Elvehjem, C. A.: Relation of Dietary Fat to Riboflavin Requirement of Growing Rats, Proc. Soc. Exper. Biol. & Med. **46**:100-104 (Jan.) 1941.

120. Kensler, C. J.; Sugiura, K.; Young, N. F.; Halter, C. R., and Rhoads, C. P.: Partial Protection of Rats by Riboflavin with Casein Against Liver Cancer Caused by Dimethylaminoazobenzene, Science **93**:308-310 (March 28) 1941.

121. Wagner, J. R.; Axelrod, A. E.; Lipton, M. A., and Elvehjem, C. A.: A Rat Assay Method for the Determination of Riboflavin, J. Biol. Chem. **136**: 357-364 (Nov.) 1940. Lingane, J. J., and Davis, O. L.: Polarographic Determination of Riboflavin (Vitamin B_2) and Other Vitamin B Factors, ibid. **137**:567-574 (Feb.) 1941. Van Duyne, F. O.: A Method for the Determination in Vitro of Riboflavin in Tissues, ibid. **139**:207-218 (May) 1941.

also have been reported.[122] Improvements in each of these methods have been suggested.

Clinical Deficiency.—Since the clinical manifestations of riboflavin deficiency were described, considerable effort has been made to discover some method by which this deficiency in man could be measured by laboratory methods. Axelrod and his associates [123] analyzed the values for riboflavin in the blood of 20 normal persons and similar values in a group of 35 patients who had varying degrees of riboflavin deficiency. Moreover, study of riboflavin in the muscles was carried out on 9 control subjects and on 30 patients who had pellagra. On the basis of their results, the authors concluded that determinations of riboflavin in the blood and muscle are of little significance in the evaluation of riboflavin deficiency in man. On the other hand, Axelrod and his group [124] in another study found that the determination of the daily excretion of riboflavin in the urine served as an aid in appraisal of the degree of riboflavin deficiency. It was shown that from 30 to 40 per cent of the vitamin was excreted in the urine of 3 persons within one hour after each had received 200 micrograms of riboflavin per kilogram of body weight. Forty-two per cent of the injected riboflavin was excreted within three hours by persons who received 400 micrograms of the vitamin per kilogram of body weight. Strong and his associates [125] found that the daily urinary excretion of riboflavin by normal adult human beings subsisting on an unrestricted diet amounted to 500 to 800 micrograms.

Although riboflavin is not abundant in many foods other than milk and meat, it has been reported [126] that it is present in citrus fruits, such as oranges and grapefruit, and in bananas and tomatoes but that little of it is found in apples or pears. Sydenstricker, Kelly and Weaver [127] recently reviewed the entire problem of ariboflavinosis. These investigators pointed out that any condition which interferes with the

122. Emmett, A. D.; Bird, O. D.; Brown, R. A.; Peacock, G., and Vandenbelt, J. M.: Determination of Vitamin B_2 (Riboflavin): Comparison of Bioassay, Microbiological, and Fluorometric Methods, Indust. & Engin. Chem. (Analyt. Ed.) **13**:219-221 (April 15) 1941.

123. Axelrod, A. E.; Spies, T. D., and Elvehjem, C. A.: Riboflavin Content of Blood and Muscle in Normal and in Malnourished Humans, Proc. Soc. Exper. Biol. & Med. **46**:146-149 (Jan.) 1941.

124. Axelrod, A. E.; Spies, T. D.; Elvehjem, C. A., and Axelrod, V.: A Study of Urinary Riboflavin Excretion in Man, J. Clin. Investigation **20**:229-232 (March) 1941.

125. Strong, F. M.; Feeney, R. E.; Moore, B., and Parsons, H. T.: The Riboflavin Content of Blood and Urine, J. Biol. Chem. **137**:363-372 (Jan.) 1941.

126. Lanford, C. F.; Finkelstein, B., and Sherman, H. C.: Riboflavin Content of Some Typical Fruits, J. Nutrition **21**:175-177 (Feb.) 1941.

127. Sydenstricker, V. P.; Kelly, A. R., and Weaver, J. W.: Ariboflavinosis, with Special Reference to the Ocular Manifestations, South. M. J. **34**:165-170 (Feb.) 1941.

proper absorption and assimilation of riboflavin may produce riboflavin deficiency. Under experimental conditions, the authors found that the injection of large amounts of nicotinic acid into patients subsisting on a diet deficient in riboflavin seemed to increase the requirement of riboflavin and to precipitate the signs of ariboflavinosis. The authors suggested that this phenomenon probably explains the high incidence of relapse among pellagrins treated with nicotinic acid without improvement of the diet. Many symptoms reported by patients who have a deficiency of riboflavin are common to all types of avitaminoses and probably are the results of multiple deficiency. Although soreness of the lips and tongue and dysphagia due to painful fissures of the commissures of the lip and tenderness of the tongue are characteristic, the authors wrote that ocular symptoms have nevertheless preceded all others among more than half their patients and that they occurred at some time among more than 90 per cent of them. Burning and itching of the eyes, photophobia, lacrimation, rapid visual fatigue, blurred vision and poor distant vision and inability to see distinctly in dim light are common specific symptoms. Usually, 5 mg. of riboflavin taken daily by mouth is adequate for rapid cure, but in the presence of gastric achlorhydria, diarrhea or severe hepatic disease 10 or 15 mg. daily may be required. In some cases the parenteral administration of 10 to 15 mg. of sodium riboflavin may be necessary. After the administration of riboflavin Sydenstricker, Kelly and Weaver observed rapid symptomatic improvement in a group of some 120 patients. Photophobia often is relieved after seventy-two hours of treatment. Glossitis is the first anatomic lesion to show changes. In a great majority of instances the tongue is restored to normal color by the third day of medication. These authors in conclusion pointed out that thus far it seems that superficial, vascular keratitis is the earliest and the most common visible manifestation of riboflavin deficiency and that it is also a rather reliable index of early deficiency of the B group of vitamins.

An interesting clinical study of riboflavin deficiency among infants and children was made by Spies and his associates.[128] These authors reported clinical, laboratory and dietary studies on 241 infants and children who had characteristic riboflavin deficiency. The authors expressed the belief that it is the most common clinical deficiency disease among infants and children in the particular area in Alabama in which deficiency diseases in general are endemic. It was pointed out that the mothers of the children studied usually had subsisted on inadequate diets during pregnancy and lactation; interestingly enough, specific treatment of a mother with riboflavin or substance rich in riboflavin was curative

128. Spies, T. D.; Bean, W. B.; Vilter, R. W., and Huff, N. E.: Endemic Riboflavin Deficiency in Infants and Children, Am. J. M. Sc. **200**:697-701 (Nov.) 1940.

for the lesions in her nursing infant. The authors observed that the average patient responded satisfactorily to the oral administration of 1 mg. of riboflavin three times a day or 1 ounce (29.6 cc.) of brewers' yeast or liver extract administered daily.

Ocular lesions resulting from deficiency of riboflavin are common among the Chinese. Only in a few cases (14 per cent of 36 cases) was cheilosis or glossitis present, and when present it was mild, according to Hou.[129] These observations differ from those reported by Sydenstricker and associates, who found that the majority of their patients who had ocular symptoms also suffered concomitantly from lesions of the lips and tongue. This same Chinese author[130] later, however, reported that cheilosis is common among Chinese refugees. Forty-four per cent of the children examined in a refugee camp were so affected.

Johnson and Eckardt[131] treated a number of patients who had active and inactive syphilitic keratitis for more than a year with riboflavin in doses of 6 to 9 mg. daily. Although these authors stressed the usefulness of riboflavin in the metabolism of tissues like the cornea and although they advised the administration of the vitamin B complex as supportive treatment in all forms of corneal ulcer, they did not find that riboflavin administered over this long period was of value in the treatment of syphilitic keratitis. A full discussion of the use of riboflavin in the treatment of keratitis and associated conditions was given by Benedict and Wagener.[132]

VITAMIN B_6 (PYRIDOXINE)

Chemical and Physiologic Properties.—Waisman and Elvehjem[133] reviewed the chemical methods for the estimation of pyridoxine. In addition, new chemical[134] and biologic[135] methods have been described.

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129. Hou, H. C.: Riboflavin Deficiency Among Chinese: I. Ocular Manifestations, Chinese M. J. **58**:616-628 (Dec.) 1940.

130. Hou, H. C.: Riboflavin Deficiency Among Chinese: II. Cheilosis and Seborrheic Dermatitis, Chinese M. J. **59**:314-325 (April) 1941.

131. Johnson, L. V., and Eckardt, R. E.: Is the Onset of Interstitial Keratitis Related to Riboflavin Deficiency? Arch. Ophth. **23**:631-632 (March) 1940; Rosacea Keratitis and Conditions with Vascularization of Cornea Treated with Riboflavin, ibid. **23**:899-907 (May) 1940; Ocular Conditions Associated with Clinical Riboflavin Deficiency, ibid. **24**:1001-1005 (Nov.) 1940.

132. Benedict, W. L., and Wagener, H. P.: Ophthalmology: Progress in Medical Science; Riboflavin and Keratitis, Am. J. M. Sc. **201**:303-309 (Feb.) 1941.

133. Waisman, H. A., and Elvehjem, C. A.: Chemical Estimation of Nicotinic Acid and Vitamin B_6, Indust. & Engin. Chem. (Analyt. Ed.) **13**:221-225 (April 15) 1941.

134. Swaminathan, M.: A Chemical Test for Vitamin B_6 in Foods, Indian J. M. Research **28**:427-439 (Oct.) 1940. Scudi, J. V.; Unna, K., and Antopol, W.: A Study of the Urinary Excretion of Vitamin B_6 by a Colorimetric Method, J.

(Footnotes continued on next page)

Henderson and his associates [136] have shown that the distribution of vitamin B_6 in foods is similar to the distribution in such foods of the other members of the vitamin B complex; kidney and muscle would appear to be the richest sources of this factor. Several other articles in which the chemistry of pyridoxine is considered are listed here by title.[137]

Experimental investigations in animals have not produced remarkable results. Street and his co-workers [138] produced severe microcytic anemia in dogs sustained on a diet deficient in vitamin B_6. This anemia regressed when vitamin B_6 was administered but did not regress when ferrous sulfate was administered. After three hundred days symptoms of cardiac decompensation, with dilatation and failure of the right ventricle, developed in the dogs. This is the picture usually associated with beriberi among human beings, but all of these animals had received sufficient thiamine.

Gross [139] investigated acrodynia in rats and its relation to pyridoxine, the filtrate factor and the essential fatty acids. He showed that the administration of any of these factors singly will not prevent some of the characteristic lesions of acrodynia and that vitamin B_6 exerts a curative action only when the animals are maintained on sufficient amounts of essential fatty acids. This agrees with the observations of György and Eckardt,[140] who have classified the cutaneous lesions of

Biol. Chem. **135**:371-376 (Sept.) 1940. Scudi, J. V.: On the Colorimetric Determination of Vitamin B_6, ibid. **139**:707-720 (June) 1941.

135. Conger, T. W., and Elvehjem, C. A.: The Biological Estimation of Pyridoxine (Vitamin B_6), J. Biol. Chem. **138**:555-561 (April) 1941.

136. Henderson, L. M.; Waisman, H. A., and Elvehjem, C. A.: The Distribution of Pyridoxine (Vitamin B_6) in Meat and Meat Products, J. Nutrition **21**:589-598 (June) 1941.

137. Scudi, J. V.; Bastedo, W. A., and Webb, T. J.: The Formation of a Vitamin B_6-Borate Complex, J. Biol. Chem. **136**:399-406 (Nov.) 1940. Harris, S. A.; Webb, T. J., and Folkers, K.: Chemistry of Vitamin B_6: I. Tautomerism, J. Am. Chem. Soc. **62**:3198-3203 (Nov.) 1940. Harris, S. A.: Chemistry of Vitamin B_6: II. Reactions and Derivatives, ibid. **62**:3203-3205 (Nov.) 1940. Harris, S. A., and Wilson, A. N.: Chemistry of Vitamin B_6: III. 2-Methyl-3-Hydroxy-4, 5-Bis-(Hydroxymethyl)-Pyridine; a Homolog of Vitamin B_6, ibid. **63**:2526-2527 (Sept.) 1941.

138. Street, H. R.; Cowgill, G. R., and Zimmerman, H. M.: Some Observations of Vitamin B_6 Deficiency in the Dog, J. Nutrition **21**:275-290 (March) 1941.

139. Gross, P.: The Role of the Unsaturated Fatty Acids in the Acrodynia (Vitamin B_6 Deficiency) of the Albino Rat, J. Invest. Dermat. **3**:505-522 (Dec.) 1940.

140. György, P., and Eckardt, R. E.: Further Investigations on Vitamin B_6 and Related Factors of the Vitamin B_2 Complex in Rats, Biochem. J. **34**:1143-1154 (Sept.) 1940.

the disease into three types, which regularly appear in rats fed vitamin B_6 without the addition of other members of the B complex. The relation of pyridoxine and the filtrate factor was further emphasized by Sullivan and Nicholls,[141] who observed severe and even gangrenous changes in the extremities of animals deficient in this vitamin.

Unna and Greslin [142] were unable to observe any toxic reaction in dogs, rabbits and rats unless the vitamin was administered in doses much larger than those ordinarily employed clinically.

Clinical Use.—There is a state of complete controversy concerning the effectiveness of vitamin B_6 in the treatment of Parkinson's disease. Supplementing previous observations, Jolliffe [143] reported definite subjective and objective improvement in 4 of 15 cases. All his failures occurred in cases in which the patient had some type of disability of more than three years' duration or in which a history of encephalitis had been given. Baker [144] observed objective improvement in 6 of 15 cases in which pyridoxine was administered intravenously and also improvement in 2 of 4 cases in which the factor was given by mouth. In direct contrast to these results, Zeligs [145] failed completely to notice any beneficial effect from administration of the factor in 15 selected cases. Barker and his associates [146] have done some accurate and well controlled work on this subject, and in 7 cases they were unable to observe "the slightest evidence of objective improvement." In addition, they investigated the urinary excretion of pyridoxine by Scudi's method and found this value to be within normal limits in all cases. Flexner and Chassin [147] found low values for the excretion of pyridoxine in 6 of 7 cases in which postencephalitic parkinsonism was present. This is not, however, in agreement with the clinical observations of Jolliffe.

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141. Sullivan, M., and Nicholls, J.: Nutritional Dermatoses in the Rat: III. Gangrene and Spontaneous Amputation of the Digits Produced by the Combined Deficiency of Vitamin B_6 and the Filtrate Components, J. Invest. Dermat. **4**:123-133 (April) 1941.

142. Unna, K., and Greslin, J.: Studies on the Toxicity and Pharmacology of Vitamin B_6 (2-Methyl-3-Hydroxy-4, 5, Bis-(Hydroxymethyl)-Pyridine), J. Pharmacol. & Exper. Therap. **70**:400-407, (Dec.) 1940.

143. Jolliffe, N.: Effects of Vitamin B_6 in Paralysis Agitans, Tr. Am. Neurol. A. **66**:54-59, 1940.

144. Baker, A. B.: Treatment of Paralysis Agitans with Vitamin B_6 (Pyridoxine Hydrochloride), J. A. M. A. **116**:2484-2487 (May 31) 1941.

145. Zeligs, M. A.: Use of Pyridoxine Hydrochloride (Vitamin B_6) in Parkinsonism, J. A. M. A. **116**:2148-2149 (May 10) 1941.

146. Barker, W. H.; Stein, H. J.; Miller, M. H., and Wintrobe, M. M.: Failure of Pyridoxine (Vitamin B_6) to Modify the Parkinsonian Syndrome, Bull. Johns Hopkins Hosp. **69**:266-275 (Sept.) 1941.

147. Flexner, J., and Chassin, M. R.: Clinical Studies on Pyridoxine (Vitamin B_6), J. Clin. Investigation **20**:313-316 (May) 1941.

Antopol and Schotland [148] administered pyridoxine to 6 patients who had pseudohypertrophic muscular dystrophy and claimed to have effected much improvement thereby. This is a problem which obviously will have to be investigated further.

PANTOTHENIC ACID

The literature of the past year on pantothenic acid is completely devoid of interest to the practicing physician who is seeking a substance that will aid in the treatment of his patients. No one has come forward with any evidence that a deficiency of this factor occurs among human beings, and such experimental work as has been done has been limited to animals.

Much confusion exists concerning the identity of pantothenic acid in relation to the liver filtrate factor, and a few writers have come to use the two terms interchangeably. Although the work of Lythgoe and his associates [149] suggests that these factors are identical, the great bulk of evidence seems to indicate that such is not the case.[150] Emerson and Evans [150a] have shown that pantothenic acid alone will alleviate some of the symptoms caused by deficiency of the liver filtrate factor in rats but that it is not so effective as a dose of the filtrate factor containing an equal amount of pantothenic acid. These observations are in general agreement with those of other investigators.[151]

Rather than become involved in a long discussion of individual experiments with animals, it seems wiser simply to list here the various results obtained and to refer the reader to the respective articles concerned. Pantothenic acid has been shown (1) to promote growth in

148. Antopol, W., and Schotland, C. E.: The Use of Vitamin B_6 in Pseudohypertrophic Muscular Dystrophy, J. A. M. A. **114**:1058-1059 (March 23) 1940.

149. Lythgoe, B.; Macrae, T. F.; Stanley, R. H.; Todd, A. R., and Work, C. E.: The Vitamin B_3 Complex of Liver: The Identity of the Liver Filtrate Factor with Pantothenic Acid, Biochem. J. **34**:1335-1340 (Nov.) 1940.

150. (*a*) Emerson, G. A., and Evans, H. M.: Growth and Graying of Rats with Total "Filtrate Factor" and with Pantothenic Acid, Proc. Soc. Exper. Biol & Med. **46**:655-658 (April) 1941. (*b*) Dimick, M. K., and Lepp, A.: Relation of Pantothenic Acid to the Filtrate Fraction of the Vitamin B Complex, J. Nutrition **20**:413-426 (Nov.) 1940. (*c*) Unna, K.: Pantothenic Acid Requirement of the Rat, ibid. **20**:565-576 (Dec.) 1941.

151. (*a*) Unna, K.: Effect of Pantothenic Acid on Growth and Reproduction of Rats on Synthetic Diet, Am. J. M. Sc. **200**:848 (Dec.) 1940. (*b*) György, P., and Poling, C. E.: Further Experiments on Nutritional Achromotrichia in Rats and Mice, Proc. Soc. Exper. Biol. & Med. **45**:773-776 (Dec.) 1940. (*c*) Frost, D. V.; Moore, R. C., and Dann, F. P.: Effect of Pantothenic Acid Alone and in Natural Products on Nutritional Achromotrichia in Rats, ibid. **46**:507-511 (March) 1941. (*d*) Footnote 150 *b* and *c*.

rats,[152] mice [153] and chicks [150b]; (2) to prevent and cure some of the lesions of nutritional achromotrichia in rats,[154] and (3) to prevent adrenal hemorrhage and necrosis in rats.[155]

Unna and Greslin [156] studied the toxicity of pantothenic acid in various animals and found that it resembled other members of the vitamin B complex in its low toxicity.

McElroy and Goss,[157] in a study of the contents of the rumina of sheep and cows, found that samples of these contents contained twenty to thirty times as much pantothenic acid as the amounts that had been fed to the animals. Furthermore, they found twice as much pantothenic acid in the milk excreted by one cow as could be accounted for in the ration the cow had been fed.

Pelczar and Porter [158] presented a microbiologic technic for the determination of pantothenic acid and studied the values for this factor in the blood of normal human beings. They found that such values ranged from 0.030 to 0.099 microgram per cubic centimeter of blood.

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152. (*a*) Zschiesche, E., and Mitchell, H. K.: Pantothenic and Hydroxy-Pantothenic Acids in Animal Nutrition, Proc. Soc. Exper. Biol. & Med. **45**:565-567 (Nov.) 1940. (*b*) Sandza, J. G., and Cerecedo, L. R.: Requirement of the Mouse for Pantothenic Acid and for a New Factor of the Vitamin B Complex, J. Nutrition **21**:609-615 (June) 1941. (*c*) Emerson and Evans.[150a] Footnote 151 *a* and *b*.

153. Lippincott, S. W., and Morris, H. P.: Pathological Changes in the Mouse Due to Pantothenic Acid Deficiency, Am. J. Path. **17**:588-589 (July) 1941. György and Poling.[151b] Sandze and Cerecedo.[152b]

154. Unna, K., and Sampson, W. L.: Effect of Pantothenic Acid on the Nutritional Achromotrichia, Proc. Soc. Exper. Biol. & Med. **45**:309-311 (Oct.) 1940. Wooley, D. W.: Relationship of Pantothenic Acid and Inositol to Alopecia in Mice, ibid. **46**:565-569 (April) 1941. Emerson and Evans.[150a] Frost, Moore and Dann.[151c]

155. Mills, R. C.; Shaw, J. H.; Elvehjem, C. A., and Phillips, P. H.: Curative Effect of Pantothenic Acid on Adrenal Necrosis, Proc. Soc. Exper. Biol. & Med. **45**:482-484 (Oct.) 1940. Salmon, W. D., and Engel, R. W.: Pantothenic Acid and Hemorrhagic Adrenal Necrosis in Rats, ibid. **45**:621-623, (Nov.) 1940.

156. Unna, K., and Greslin, J.: Toxicity of Pantothenic Acid, Proc. Soc. Exper. Biol. & Med. **45**:311-312 (Oct.) 1940; Studies on the Toxicity and Pharmacology of Pantothenic Acid, J. Pharmacol. & Exper. Therap. **73**:85-90 (Sept.) 1941.

157. McElroy, L. W., and Goss, H.: A Quantitative Study of Vitamins in the Rumen Content of Sheep and Cows Fed Vitamin-Low Diets: IV. Pantothenic Acid, J. Nutrition **21**:405-409 (April) 1941.

158. Pelczar, M. J., Jr., and Porter, J. R.: A Microbiological Assay Technique for Pantothenic Acid with the Use of "Proteus Morganii," J. Biol. Chem. **139**:111-119 (May) 1941; Determination of Pantothenic Acid in Normal Blood and Urine by Microbiological Technic, Proc. Soc. Exper. Biol. & Med. **47**:3-7 (May) 1941.

with an average value of 0.059 microgram per cubic centimeter, and that the normal daily excretion of pantothenic acid in the urine varied from 1.46 to 6.79 mg., with an average value for such excretion of 3.81 mg.

ASCORBIC ACID (VITAMIN C)

Chemical and Physiologic Properties.—Last year two of us (H. R. B. and W. V. L.) reviewed several articles in which strong evidence was presented that ascorbic acid had an enzyme function. Results of subsequent investigations have placed this possibility on even stronger ground. Levine, Marples and Gordon [159] have shown that if premature infants are fed diets relatively high in protein they exhibit a spontaneous defect in their metabolism of tyrosine and phenylalanine, excreting l-parahydroxyphenyllactic acid and parahydroxyphenylpyruvic acid in the urine, rather than homogentisic acid, as in the case of alkaptonuria. They were able to remedy this metabolic defect promptly by the administration of ascorbic acid.[160] In the course of their efforts to prove the specificity of ascorbic acid in abolishing this metabolic error, they were unable to demonstrate any similar effect exerted by other substances, including all members of the vitamin B complex. Sealock, Perkinson and Basinski [161] supplemented these observations with results obtained in investigations on animals and demonstrated that vitamin C had a parallel function in guinea pigs. Rothman [162] has shown ascorbic acid to have an influence in vitro on the oxidation and oxidation products of tyrosine in that it greatly furthers the formation of dihydroxyphenylalanine (dopa) and prevents its further oxidation. There seems to be justification, then, for the statement by Levine, Gordon and Marples [160] that these "observations do establish beyond any doubt the key position of vitamin C in the metabolism of aromatic amino acids in the growing human organism." They expressed the belief that the detection of the various intermediary products in the urine may serve as a valuable aid in the early detection of deficiency of vitamin C among premature and young infants and that disappearance of such products from the urine may serve as the earliest sign of healing.

159. Levine, S. Z.; Marples, E., and Gordon, H. H.: A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants: I. Identification and Assay of Intermediary Products, J. Clin. Investigation **20**:199-207 (March) 1941.

160. Levine, S. Z.; Gordon, H. H., and Marples, E.: A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants: II. Spontaneous Occurrence and Eradication by Vitamin C, J. Clin. Investigation **20**:209-219 (March) 1941.

161. Sealock, R. R.; Perkinson, J. D., Jr., and Basinski, D. H.: Further Analysis of the Rôle of Ascorbic Acid in Phenylalanine and Tyrosine Metabolism, J. Biol. Chem. **140**:153-160 (July) 1941.

162. Rothman, S.: Influence of Ascorbic Acid on Oxidation of Tyrosine by Ultraviolet Light, Proc. Soc. Exper. Biol. & Med. **45**:52-54 (Oct.) 1940.

Whether this will prove to be the case is obviously a subject concerning which nothing more than conjecture can be exercised now; it seems apparent, however, that the time is not far distant when investigators will present answers to the problem of the fundamental role of vitamin C in the metabolism of the body. In this same paper [160] are offered some of the new questions which arise as a direct result of this work:

> What is the relation, if any, between the demonstrated defect in the metabolism of tyrosine and phenylalanine and the morphologic changes characteristic of vitamin C deficiency, namely, improper formation of intercellular substance and collagen? Since tyrosine is a precursor of both thyroxine and adrenalin, may the presence of the defect in premature infants contribute, under certain conditions, to their instability of body temperature regulation? Is the delicate transparency of the skin of premature infants related to improper utilization of melanin, another product of tyrosine? Does the observed increased excretion of aromatic organic acids in premature infants fed cow's milk play a role in their known tendency to develop severe rickets? If so, this observation may explain, in part at least, the frequently postulated importance of vitamin C in the development of rickets.

Harrer and King [163] studied the effects of deficiency of ascorbic acid on two hydrolytic enzymes and two respiratory enzymes in guinea pigs. As the vitamin was depleted, hepatic esterase activity was observed to decrease progressively to — 65 per cent in cases of acute scurvy. They were unable to obtain any evidence, however, that ascorbic acid is a part of the enzyme, as has been claimed by other authors. There was only a moderate degree of change in the phosphatase activity of the intestinal mucosa and the renal cortex. They demonstrated a marked decrease in the succinic dehydrogenase activity of cardiac and skeletal muscles as scurvy developed but only a moderate decrease in the content of cytochrome oxidase in these muscles.

Fan and Woo [164] administered vitamin C to a patient who had glycogen disease and observed a pronounced increase in the urinary excretion of creatine and creatinine. This effect was not obtained among normal children, because, the authors stated, any increase in the formation of creatine due to ascorbic acid was covered by the normal capacity for storage. The relation of vitamin C metabolism to creatine metabolism is not understood.

Schwachman [165] has carried out some interesting studies on serum phosphatase in 18 cases of infantile scurvy; he found abnormally low values in cases of acute scurvy (average value, 3.2 Bodansky units, as

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163. Harrer, C. J., and King, C. G.: Ascorbic Acid Deficiency and Enzyme Activity in Guinea Pig Tissues, J. Biol. Chem. **138**:111-121 (March) 1941.

164. Fan, C., and Woo, T. T.: Effect of Vitamin C on Creatine and Creatinine Metabolism, Proc. Soc. Exper. Biol. & Med. **45**:90-92 (Oct.) 1940.

165. Schwachman, H.: Serum Phosphatase in Infantile Scurvy, J. Pediat. **19**:38-41 (July) 1941.

compared with a normal mean value of 7.2 Bodansky units), with a substantial increase in serum phosphatase within a week after the beginning of ascorbic acid therapy. As he pointed out, this is to be expected, since previous evidence suggests that bone is the major source of serum phosphatase, and that this enzyme may serve as an index of osteoblastic activity. In rickets the high value for phosphatase in the serum commonly encountered reflects the picture of osteoblastic overactivity, whereas in scurvy the pathologic picture is that of inactivity or inability of the osteoblasts to form a bony matrix.

Recent claims for the value of vitamin C in the treatment of habitual abortion led Israel and Meranze [166] to investigate the effect of ascorbic acid on the endometrium of various animals. They found that the endometrium of the vitamin-treated animals approximated the changes in a progesterone-controlled group.

Basu and Biswas [167] and Basu and Ray [168] presented evidence derived from experiments on human beings which indicates that vitamin C augments muscular contraction, produces quicker relaxation and delays the onset of fatigue. Results of these studies await both experimental and clinical confirmation.

Metabolism of Vitamin C.—For a more complete summary of the metabolism of vitamin C, the reader is referred to an excellent review by Farmer.[169] Milhorat, Bartels and Toscani [170] demonstrated that the liver plays an important role in the metabolism of ascorbic acid, since a definite increase in the excretion of this acid followed hepatic injury caused by the inhalation of chloroform. In a subsequent study they and an associate [171] observed that shivering and the administration of epinephrine likewise produced an increased excretion of ascorbic acid in the urine. These observations tend to suggest that the metabolism of vitamin C may be related to that of glycogen. Such a relation would

166. Israel, S. L., and Meranze, D. R.: Progesterone-Like Effect of Ascorbic Acid (Vitamin C) on the Endometrium, Endocrinology **29**:210-214 (Aug.) 1941.

167. Basu, N. M., and Biswas, P.: The Influence of Ascorbic Acid on Contractions and the Incidence of Fatigue on Different Types of Muscles, Indian J. M. Research **28**:405-417 (Oct.) 1940.

168. Basu, N. M., and Ray, G. K.: Effect of Vitamin C on the Incidence of Fatigue in Human Muscles, Indian J. M. Research **28**:419-426 (Oct.) 1940.

169. Farmer, C. J.: Vitamin C Analysis in Relation to Clinical Problems, Quart. Bull. Northwestern Univ. M. School **14**:220-235, 1940.

170. Milhorat, A. T.; Bartels, W. E., and Toscani, V.: Effect of Hepatic Injury on Vitamin C Excretion in Fasting Dogs, Proc. Soc. Exper. Biol. & Med. **45**:394-397 (Oct.) 1940.

171. Milhorat, A. T.; Hardy, J. D.; Bartels, W. E., and Toscani, V.: Effect of Shivering, Iodoacetate, and Epinephrine on Vitamin C and Creatine Excretion in Fasting Dogs, Proc. Soc. Exper. Biol. & Med. **45**:397-399 (Oct.) 1940.

explain the statement by Ralli and Sherry [172] that the ascorbic acid content both of the blood and of the urine of diabetic dogs was decreased by the administration of insulin, although these investigators have since shown that this effect was caused by a redistribution of ascorbic acid in the elements of the blood.[173]

Ritz, Samuels and Addiss [174] have shown that salicylates and carvone cause an increased excretion of ascorbic acid in the urine of rats. Their results would seem to indicate that whereas salicylates produced this effect through loss from the tissues, carvone brought about an increased production of vitamin C. Drake, Gruber and Haury [175] administered sodium 5,5-diphenylhydantoinate (dilantin sodium) to rats and observed an increased urinary excretion of ascorbic acid accompanied by a diminution in the supply of the acid in the body of the animals.

Methods Used in the Diagnosis of Deficiency of Ascorbic Acid.—Results of investigations of the value of determinations of ascorbic acid in the plasma have served to push such determinations into almost total disrepute.[176] So-called scurvy levels (less than 0.4 mg. per hundred cubic centimeters of plasma) are found so commonly among healthy persons that any diagnosis of "subclinical vitamin C deficiency" (a condition of questionable authenticity in any event) based solely on this laboratory procedure rests on uncertain footing. More reliable are determinations of the concentration of ascorbic acid in the whole blood,

172. Ralli, E. P., and Sherry, S.: Effect of Insulin on Plasma Level and Excretion of Vitamin C, Proc. Soc. Exper. Biol. & Med. **43**:669-672 (April) 1940.

173. Ralli, E. P., and Sherry, S.: The Effect of Insulin on the Metabolism of Vitamin C, Am. J. Physiol. **133**:p418-p419 (June) 1941.

174. Ritz, N. D.; Samuels, L. T., and Addiss, G.: The Effect of Salicylates and Carvone on the Ascorbic Acid Content of Animal Tissue, J. Pharmacol. & Exper. Therap. **70**:362-369 (Dec.) 1940.

175. Drake, M. E.; Gruber, C. M., and Haury, V. G.: Effects of Sodium Diphenyl Hydantoinate (Dilantin) on Vitamin C Level in Tissues and Vitamin C Excretion in Rats, J. Pharmacol. & Exper. Therap. **71**:268-272 (March) 1941.

176. Minnich, V.; Wright, S. T.; Moore, C. V., and Spies, T. D.: Whole Blood and Plasma Ascorbic Acid Concentrations in Patients with Pellagra and Associated Deficiency Diseases, Proc. Soc. Exper. Biol. & Med. **45**:441-446 (Oct.) 1940. Mindlin, R. L.: Concentration of Ascorbic Acid in the Plasma During the Treatment of Infantile Scurvy, J. Pediat. **17**:621-625 (Nov.) 1940. Kastlin, G. J.; King, C. G.; Schlesinger, C. R., and Mitchell, J. W.: Chemical Methods for the Determination of Clinical Vitamin C (Ascorbic Acid) Deficiency, Am. J. Clin. Path. **10**:882-893 (Dec.) 1940. Holmes, F. E.; Cullen, G. E., and Nelson, W. E.: Levels of Ascorbic Acid in the Blood Plasma of Apparently Healthy Children, J. Pediat. **18**:300-309 (March) 1941. Crane, M. M., and Woods, P. W.: A Study of Vitamin C Nutrition in a Group of School Children: Clinical and Laboratory Studies, New England J. Med. **224**:503-509 (March 20) 1941. Milam, D. F., and Wilkins, W.: Plasma Vitamin C Levels in a Group of Children Before and After Dietetic Adjustment, Am. J. Trop. Med. **21**:487-491 (May) 1941.

the white cell–platelet fraction or the response of the content of ascorbic acid in the plasma to the parenteral administration of the acid. Even the last method is open to question, since it produces information concerning only the degree of saturation of the organism with the vitamin.

Butler and Cushman have continued their excellent studies of last year, in which they demonstrated that ascorbic acid reaches its highest concentrations in the buffy layer of the blood. They [177] have recently shown that the reducing property of metaphosphoric acid extracts both of leukocytes and of platelets fulfils the chemical criteria for ascorbic acid and that this property appears to depend on some constituent of a not readily diffusible chemical complex. They have further shown that the concentration of this substance depends on the presence of ascorbic acid in the diet and provides an index to deficiency of ascorbic acid which is physiologically significant.

Heinemann [178] has continued his studies on the transference of ascorbic acid from serum to cells and has demonstrated that the partition is not governed by the laws of simple diffusion. Further than this, he has shown [179] that leukoctyes in the serum enhance the determination of ascorbic acid, as opposed to erythrocytes, which exert a definite stabilizing effect. There is much greater diffusion of ascorbic acid from serum to leukocytes than to erythrocytes, although Heinemann did not imply that leukocytes do not contain ascorbic acid in vivo. Ralli and Sherry [173] have confirmed Heinemann's observations in their work on pancreatectomized dogs. In a previous communication [172] they reported that they had found the administration of insulin to decrease values for ascorbic acid in the plasma; reassessment of this judgment in the light of newer methods has shown this effect to be one of redistribution of the ascorbic acid in the various constituents of the blood.

Those interested in the chemical and the polarographic determination of ascorbic acid will find these subjects well presented by King [180] and Kirk.[181] Ballentine [182] presented a new method for the chemical determination of ascorbic acid in citrus fruit juices.

177. Butler, A. M., and Cushman, M.: An Ascorbic Acid-Like Reducing Substance in the Buffy Layer of Centrifuged Oxalated Blood, J. Biol. Chem. **139**:219-226 (May) 1941.

178. Heinemann, M.: Distribution of Ascorbic Acid Between Cells and Serum of Human Blood, J. Clin. Investigation **20**:39-46 (Jan.) 1941.

179. Heinemann, M.: Influences of Erythrocytes and of Leukocytes on Stability and Transfer of Ascorbic Acid in Human Blood, J. Clin. Investigation **20**:467-471 (Sept.) 1941.

180. King, C. G.: Chemical Methods for Determination of Vitamin C, Indust. & Engin. Chem. (Analyt. Ed.) **13**:225-227 (April 15) 1941.

181. Kirk, M. M.: Polarographic Determination of Ascorbic Acid, Indust. & Engin. Chem. (Analyt. Ed.) **13**:625-626 (Sept. 15) 1941.

182. Ballentine, R.: Determination of Ascorbic Acid in Citrus Fruit Juices, Indust. & Engin. Chem. (Analyt. Ed.) **13**:89 (Feb. 15) 1941.

Data on Clinical Use.—The literature of 1940 seemed to give strong support to the concept that vitamin C has an important role in the healing of wounds. To say that the past year has been a disappointment in this particular respect would constitute an understatement. Save for an excellent piece of experimental work by Hunt,[183] clinical investigators seem to have abandoned a subject which may prove to be of value in the future. Hunt has presented strong support for the theory that ascorbic acid is concerned in the formation of intercellular material. He has shown that this substance appears late and remains in the precollagenous state in experimentally produced wounds of subscorbutic guinea pigs, with a resultant loss in tensile strength of the scars. The mature collagen of well healed scars reverted to precollagen when vitamin C was withdrawn from the diet of the animals. In animals deficient in vitamin C there was a tendency toward the formation of hematomas which were not absorbed or organized in the normal manner. Lack of ascorbic acid seemed to delay the absorption of catgut ligatures in experimentally produced wounds. In a single experiment involving a human being there was no difference between the healing of wounds in the presence of deficiency of vitamin C and the healing of wounds in a state of saturation. The period of deprivation, however, was only three months, a period which Crandon, Lund and Dill [184] have shown is insufficient for the production of changes in healing in a previously normal person. Data obtained at necropsy as presented by Hunt are not convincing and need further study. Of 18 patients who died eight or more days after operation, 8 had microscopic changes in their wounds similar to those which occurred in the wounds of subscorbutic guinea pigs. Knowledge of the status of vitamin C nutrition in these particular patients was not sufficient to permit the formation of unreserved conclusions. More significant is the fact that Hunt has been able to reduce the disruption of wounds among his patients by 75 per cent since the preoperative administration of ascorbic acid has become a routine measure. Although he himself criticizes this figure, on the ground that other uncontrolled factors entered into it, it seems noteworthy that in the wounds which failed to heal there was always gross local infection or ischemic necrosis.

Two interesting studies on the relation of vitamin C to the blood-forming organs have appeared during the past year. Liu and his associates [185] divided 6 anemic boys in an institution into two groups,

183. Hunt, A. H.: The Role of Vitamin C in Wound Healing, Brit. J. Surg. **28**:436-461 (Jan.) 1941.

184. Crandon, J. H.; Lund, C. C., and Dill, D. B.: Experimental Human Scurvy, New England J. Med. **223**:353-369 (Sept. 5) 1940.

185. Liu, S. H.; Chu, H. I.; Yu, T. F.; Hsu, H. C., and Cheng, T. Y.: Anemia in Vitamin C Deficiency and Its Response to Iron, Proc. Soc. Exper. Biol. & Med. **46**:603-606 (April) 1941.

administering ascorbic acid to the members of one group and ferrous carbonate to the members of the other. At the end of four weeks it was found that whereas ascorbic acid had raised values for this factor in the plasma to normal, no appreciable changes had occurred in the hemoglobin content, the erythrocyte counts or the hematocrit readings. In contrast to this uniform failure, members of the iron-treated group responded in most cases with a significant increase in these values, despite the persistence of low values for ascorbic acid in the plasma. This agrees with the observations of Lozner [186] and seems to indicate that scorbutic anemia probably is not due to lack of vitamin C itself but is more likely related to a concomitant deficiency of iron.

Stimulated by Barrow's theory that one of the functions of vitamin C is to maintain the concentration of hemoglobin in the blood at a normal value, Deeny [187] administered ascorbic acid and sodium bicarbonate to 2 patients who had polycythemia and reported encouraging results. He was unable to obtain any effect from the administration of ascorbic acid alone.

Cormia [188] and Vail [189] reported that favorable results followed the use of ascorbic acid in diminishing sensitivity to arsenic in antisyphilitic therapy. McDonald and Johnson [190] were unable to establish any relation in guinea pigs between the quantity of ascorbic acid administered parenterally or values for ascorbic acid in the blood and the sensitivity to the repeated intradermal injection of neoarsphenamine.

Goldsmith and associates [191] have presented data to indicate that in the presence of bronchial asthma the requirement of vitamin C is increased. Of 29 patients, subnormal values for ascorbic acid in the plasma were observed in 19, and it was found to be more difficult to maintain values for ascorbic acid in the blood of patients who had bronchial asthma. In 2 patients there seemed to be reverse parallelism between the level of ascorbic acid in the blood and the frequency and

186. Lozner, E. L.: Studies on Hemoglobin Regeneration in Patients with Vitamin C Deficiency, New England J. Med. **224**:265-268 (Feb. 13) 1941.

187. Deeny, J.: Polycythemia and Vitamin C, Brit. M. J. **2**:864-866 (Dec. 21) 1940.

188. Cormia, F. E.: Postarsphenamine Dermatitis: The Relation of Vitamin C to the Production of Arsphenamine Sensitiveness, and Its Use as an Adjunct to Further Arsphenamine Therapy in Patients with Cutaneous Hypersensitiveness to the Arsphenamines, J. Invest. Dermat. **4**:81-93 (Feb.) 1941.

189. Vail, A. D.: Influence of Vitamin C Therapy on Arsenical Sensitivity, J. Missouri State M. A. **38**:110-120 (April) 1941.

190. McDonald, F. M., and Johnson, H. H.: Ascorbic Acid and Arsphenamine Dermatitis: An Experimental Study, Arch. Dermat. & Syph. **43**:682-688 (April) 1941.

191. Goldsmith, G. A.; Ogaard, A. T., and Gowe, D. F.: Vitamin C (Ascorbic Acid) Nutrition in Bronchial Asthma: An Estimation of the Daily Requirement of Ascorbic Acid, Arch. Int. Med. **67**:597-608 (March) 1941.

severity of the attacks. Any beneficial effect obtained was probably nonspecific, however, since 5 other patients were not benefited by administration of the vitamin.

Ludden, Flexner and Wright [192] conducted careful studies on the absorption of vitamin C by patients who had gastrointestinal disturbances. They were unable to demonstrate interference with such absorption in the presence of gastric lesions, since ascorbic acid seems to be absorbed in the intestinal tract. The authors stated that they plan to report a case in which the entire jejunum and all but the terminal 6 to 8 inches (15 to 20 cm.) of ileum were resected; it was necessary for the patient to receive 35 Gm. of ascorbic acid before the value for the vitamin in the plasma could be increased to 0.7 mg. per hundred cubic centimeters, and for maintenance of such a value a daily dose of 700 mg. per hundred cubic centimeters was required. Three patients requiring increased maintenance doses were suffering from hypermotility of the gastrointestinal tract. Contrary to an accepted belief, achlorhydria and alkali therapy failed to interfere with absorption.

Marchmont-Robinson [193] conducted a survey on the effects of the administration of vitamin C to lead workers. Carefully controlled studies of basophilic aggregation counts, urinary excretion of lead and subjective symptoms seemed to indicate that a beneficial effect of some extent proceeds from such therapy. He could find no evidence that ascorbic acid promotes the storage of lead; rather, he suggested that the reverse is true. His conclusion, however, that the absorption of lead produces avitaminosis C and that the symptoms of chronic lead poisoning are due to subclinical scurvy seems hardly justifiable.

During the past year favorable reports have appeared on the use of vitamin C in cases of radiation sickness,[92] gingivitis,[194] inflammatory corneal conditions [195] and pain in the temporomandibular region.[196]

Hofmeyr [197] made a rather extensive study of ascorbic acid metabolism among the Negroes of South Africa and reviewed the importance

192. Ludden, J. B.; Flexner, J., and Wright, I. S.: Studies on Ascorbic Acid Deficiency in Gastric Diseases: Incidence, Diagnosis and Treatment, Am. J. Digest. Dis. **8**:249-252 (July) 1941.

193. Marchmont-Robinson, S. W.: Effect of Vitamin C on Workers Exposed to Lead Dust, J. Lab. & Clin. Med. **26**:1478-1481 (June) 1941.

194. Campbell, H. G., and Cook, R. P.: Treatment of Gingivitis with Ascorbic Acid, Brit. M. J. **1**:360-361 (March 8) 1941.

195. Lyle, T. K., and McLean, D. W.: Vitamin "C" (Ascorbic Acid)—Its Therapeutic Value in Inflammatory Conditions of the Cornea, Brit. J. Ophth. **25**:286-295 (June) 1941.

196. Sinclair, J. A.: Vitamin C Deficiency: A Factor in Producing Subluxation, Pain in the Temporomandibular Area and Other Dental Involvements, Dental Items Interest **63**:313-317 (April) 1941.

197. Hofmeyr, H. O.: Unpublished data.

which ascorbic acid nutrition played in the early establishment of civilization in this part of Africa.

Human Requirements and Sources.—Hathaway and Meyer [198] found the marginal level of the daily intake of ascorbic acid in 4 children of preschool age to be 30 mg. Goldsmith, Ogaard and Gowe [199] administered 50 mg. of ascorbic acid daily to 12 ambulatory patients and found that this amount was sufficient to maintain a value for ascorbic acid in the blood of 1 mg. per hundred cubic centimeters for seven to eighteen weeks. These, however, are isolated figures, and the recommended allowance for this vitamin was set at higher values than these by the Committee on Food and Nutrition of the National Research Council (see table).

Holmes, Pigott and Tripp [200] conducted an interesting study on the relative costs of various sources of vitamin C and found canned orange juice, canned grapefruit juice, fresh orange juice and fresh grapefruit juice to be the cheapest, in the order named. Other interesting and valuable studies on sources of vitamin C are listed here.[201]

VITAMIN D

Chemical and Physiologic Properties.—It has been recognized for many years that vitamin D probably exerts its antirachitic properties through its ability to increase the concentration of phosphate in the serum. Previous studies have shown that this elevation is effected by increase in the intestinal absorption and diminution in the urinary excretion of phosphates. Harrison and Harrison [202] recently have investigated this urinary excretion of phosphates in dogs and have been able to show that in rachitic dogs there is a diminution in tubular reabsorption. After the administration of vitamin D they observed a rapid increase in this reabsorption, the rate of glomerular filtration remaining unchanged. These observations suggest that refractory rickets may have a basis in

198. Hathaway, M. L., and Meyer, F. L.: Studies on the Vitamin C Metabolism of Four Preschool Children, J. Nutrition **21**:503-514 (May) 1941.

199. Goldsmith, G. A.; Ogaard, A. T., and Gowe, D. F.: Estimation of the Ascorbic Acid (Vitamin C) Requirement of Ambulatory Patients, Arch. Int. Med. **67**:590-596 (March) 1941.

200. Holmes, A. D.; Pigott, M. G., and Tripp, F.: Comparative Costs of Vitamin C in Fresh and Commercially Canned Fruit and Vegetable Juices, New England J. Med. **225**:68-73 (July 10) 1941.

201. Keller, M. L., and Minot, A. S.: "Pot Liquor": A Neglected Source of Vitamin C for the Feeding of Infants, South. M. J. **34**:163-164 (Feb.) 1941. Vitamin C for the Baby, Annotations, Lancet **1**:48 (Jan. 11) 1941. Chappell, G.: The Distribution of Vitamin C in Foods Sold on the Open Market, J. Hyg. **40**:699-732 (Dec.) 1940.

202. Harrison, H. E., and Harrison, H. C.: The Renal Excretion of Inorganic Phosphate in Relation to the Action of Vitamin D and Parathyroid Hormone, J. Clin. Investigation **20**:47-55 (Jan.) 1941.

permanently damaged tubular epithelium, which will no longer respond to stimulation by vitamin D. The effect of parathyroid extract in lowering the serum phosphate was shown to occur by means of diminution of the tubular reabsorption of this ion.

That the bony changes in rickets are merely consequences of disturbances in the calcium and phosphorus of the serum has been assumed in the past. Kraemer and his associates [203] have presented evidence that this may not be entirely the case. In a preliminary report of results of studies in vitro on the bones of rachitic and nonrachitic rats, they have shown that vitamin D seems to exert some type of direct effect on bone. Bones of deficient animals did not take up calcium and phosphorus salts from incubation solutions as rapidly as did normal bones and gave up more of these bone-forming salts into solutions containing none of these ions. These observations may lead to revolutionary changes in the present concept of the pathologic physiology of rickets.

Shohl and Farber [204] studied the effect of dihydrotachysterol in high calcium, low phosphorus rickets of rats. Although they were able to effect a cure by administration of this compound, they found vitamin D to be four hundred times as effective and only a fifth as toxic. They observed that dihydrotachysterol resembles vitamin D in its action and differs from parathyroid in that it increases calcium absorption and diminishes the urinary excretion of phosphate. These observations agree with the hypothesis presented in 1938 by Albright and associates.[205]

The reader will find an excellent summary of the subject of calcium and phosphorus metabolism and its relation to vitamin D and the parathyroid glands in a recent paper by Leverton.[206]

Opper [207] demonstrated by means of experimentation with animals that renal damage is an important factor in the production of toxicity arising from overdosage with vitamin D. His most significant observation was a high value for phosphate in the serum, there being little variation in values for serum calcium among normal control animals.

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203. Kraemer, V. V.; Landtman, B., and Simola, P. E.: In Vitro Studies on the Role of Vitamin D in the Metabolism of Calcium and Phosphorus in the Rat Bones, Acta physiol. Scandinav. **1**:285-298, 1940.

204. Shohl, A. T., and Farber, S.: Effect of A. T. 10 (Dihydrotachysterol) on Rickets in Rats Produced by High-Calcium-Low-Phosphorus Diets, J. Nutrition **21**:147-154 (Feb.) 1941.

205. Albright, F.; Bloomberg, E.; Drake, T., and Sulkowitch, H. W.: A Comparison of the Effects of A. T. 10 (Dihydrotachysterol) and Vitamin D on Calcium and Phosphorus Metabolism in Hypoparathyroidism, J. Clin. Investigation **17**:317-329 (May) 1938.

206. Leverton, W. R.: Parathormone and Vitamin D: Calcium and Phosphorus Metabolism, M. Bull. Vet. Admin. **17**:266-273 (Jan.) 1941.

207. Opper, L.: Effect of Renal Damage on the Toxicity of Hypervitaminosis D in Rats, Arch. Path. **31**:569-577 (May) 1941.

This observation is of importance when it is recalled that one of the earliest signs of renal insufficiency is elevation of the value for serum phosphorus.

New methods for the assay of vitamin D continue to appear,[208] and Milas, Heggie and Raynolds [209] have presented a good summary of previous work, with detailed procedures.

Clinical Use.—Readers interested in the subject of vitamin D therapy will find Kramer's [210] paper a complete survey. The past year has not been particularly productive in the field of clinical investigation. Liu and his associates [211] have continued their fine work along this line. In a study of female patients who had osteomalacia they were unable to find any inherent inability of these patients to retain minerals during pregnancy. They proved conclusively that in the absence of adequate supplies of calcium and vitamin D pregnancy and lactation are important factors in demineralization of the skeleton. They expressed the opinion that of these two substances vitamin D is probably the more important, provided that there is a reasonable intake of calcium.

Vollmer [212] reported observations made at necropsy concerning a 3 year old child who had received crystalline vitamin D_3 (2,260,000 U. S. P. units of vitamin D) within twenty-six days of its death. Detailed study did not reveal any changes which could be ascribed to hypervitaminosis D. Similar negative observations were made concerning a child who received an equivalent of 1,260,000 units of vitamin D within nine days before death. Bioassay failed to reveal any vitamin D in the brains of these patients, in contradiction to the results of Windorfer, who found that 4 per cent of the vitamin D that had been administered was present in the brain.

208. Martin, G. J.: The Use of Osteotropic Dyes in a Modified Line Test for Vitamin D, J. Lab. & Clin. Med. **26**:714-719 (Jan.) 1941. Loy, H. W., Jr.; DeWitt, J. B., and Knudsen, L. F.: Observations on the Chick Method for the Assay of Vitamin D: I. Relative Accuracy of Group and Individual Ashing Procedures and Relation of Chick Weight to Per Cent Bone Ash, J. A. Offic. Agric. Chemists **24**:190-196 (Feb.) 1941.

209. Milas, N. A.; Heggie, R., and Raynolds, J. A.: A Spectroscopic Method for the Quantitative Estimation of Vitamin D, Indust. & Engin. Chem. (Analyt. Ed.) **13**:227-231 (April 15) 1941.

210. Kramer, B.: Vitamin D Therapy, J. Mt. Sinai Hosp. **8**:188-209 (Sept.-Oct.) 1941.

211. Liu, S. H.; Chu, H. I.; Hsu, H. C.; Chao, H. C., and Cheu, S. H.: Calcium and Phosphorus Metabolism in Osteomalacia: XI. The Pathogenetic Role of Pregnancy and Relative Importance of Calcium and Vitamin D Supply, J. Clin. Investigation **20**:255-271 (May) 1941.

212. Vollmer, H.: Distribution of Vitamin D in the Brain After Repeated Administration of Massive Doses: Histologic Investigation of D-Hypervitaminosis, Arch. Pediat. **58**:9-20 (Jan.) 1941.

Wagner and Jones [213] applied viosterol in oil to the skin of a small group of infants and demonstrated roentgenographic evidence of healing rickets. The amounts required were much greater than those customarily employed in oral administration, and the authors did not recommend routine administration of viosterol in such a manner. They stated that it may serve as a route of administration to patients who exhibit defects in gastrointestinal absorption.

Two reports on the use of vitamin D in psoriasis have appeared; Krafka [214] claimed good results, and Wright [215] expressed the opinion that vitamin D is not specific for this disease and that it may give rise to reactions.

VITAMIN E

Chemical and Physiologic Properties.—Although there has been assembled a large amount of data on this subject, investigations of the chemical aspects of vitamin E and investigations involving experimentation with animals have not been particularly fruitful. Several articles in which the chemistry of the tocopherols were discussed are listed here.[216]

Friedman and Mattill [217] studied the consumption of oxygen by the skeletal muscles of vitamin E–deficient rats and found it was as high as 40 per cent above normal in young animals without dystrophy and slightly elevated in older rats with dystrophy. The administration of

213. Wagner, E. A., and Jones, D. V.: Observations on the Application of Vitamin D to the Skin, Ohio State M. J. **37**:249-254 (March) 1941.

214. Krafka, J.: Vitamin D Therapy in Psoriasis, J. M. A. Georgia **30**:398-400 (Sept.) 1941.

215. Wright, C. S.: Vitamin D Therapy in Dermatology, Arch. Dermat. & Syph. **43**:145-154 (Jan.) 1941.

216. Ridgway, R. R.; Drummond, J. C., and Wright, M. D.: The Biological Activity of the Oxidation Products of α-Tocopherol, Biochem. J. **34**:1569-1573, 1940. Smith, L. I.; Wawzonek, S., and Miller, H. C.: The Chemistry of Vitamin E: XXVI. 5-Hydroxy-4, 6, 7-Trimethylcoumaran, 5-Hydroxy-2, 2, 4, 6, 7-Pentamethylcoumaran, 6-Hydroxy-2, 2, 5-Trimethyl-7, 8-Benzochroman, and 5-Hydroxy-2, 4-Dimethyl-6, 7-Benzocoumaron, J. Organic Chem. **6**:229-235 (March) 1941. Smith, L. I.; Ruoff, P. M., and Wawzonek, S.: The Chemistry of Vitamin E: XXVII. Oxidation of Hydroquinones, *p*-Hydroxychromans and *p*-Hydroxycoumarans to Quinones with Ceric Sulfate, ibid. **6**:236-241 (March) 1941. Smith, L. I., and Opie, J. W.: The Chemistry of Vitamin E.: XXVIII. (1) Synthesis of the Three Dimethylethylquinones, ibid. **6**:427-436 (May) 1941. Smith, L. I.; Kolthoff, I. M.; Wawzonek, S., and Ruoff, P. M.: The Chemistry of Vitamin E: XXIX. Studies of the Behavior of Compounds Related to Vitamin E at the Dropping Mercury Electrode, J. Am. Chem. Soc. **63**:1018-1024 (April) 1941. Tishler, M., and Evans, H. M.: Vitamin E Activities of Some Compounds Related to α-Tocopherol, J. Biol. Chem. **139**:241-245 (May) 1941.

217. Friedman, I., and Mattill, H. A.: The Oxygen Consumption of Skeletal Muscle from Animals Deprived of Vitamin E, Am. J. Physiol. **131**:595-600 (Jan.) 1941.

alpha tocopherol lowered this consumption within twenty-four hours. These authors recalled the suggestion of Szent-Györgyi that there exists in animal tissues a series of biocatalysts which accomplish the gradual degradation of a metabolite to such an extent that its total energy is released stepwise, rather than completely at a single bound. They then postulated that in the absence of tocopherol one of the intermediate and delaying steps may drop out, with the result that oxidation proceeds more rapidly. Support is lent to this theory if it is recalled that results of in vitro experiments have shown alpha tocopherol to possess anti-oxidation properties.

Krakower and Axtmayer [218] have shown that certain muscular lesions in rats formerly thought to be related to avitaminosis A actually are results of deficiency of tocopherol. Beard and Pizzolato [219] were able to increase the creatine content of the muscles of rats by 20 to 36 per cent by means of the administration of vitamin B_6, nicotinic acid and vitamin E and concluded that these substances must be considered as necessary for normal muscle metabolism. Holmes and Pigott [220] produced definite improvement in vitamin E–deficient rats which had muscular dystrophy by the administration of thiamine hydrochloride. Mackenzie and McCollum [221] demonstrated the skeletal muscles of the male rabbit to be more sensitive to deficiency of vitamin E than the testes, in contrast to the opposite reaction in rats.

Biddulph and Meyer [222] studied the effect of deprivation of vitamin E on the endocrine glands of rats, with no impressive results. The usual testicular degeneration appeared, but there was no effect on ovarian size or function. The thyroid glands of male rats increased as much as 100 per cent, but there were no striking changes in any other glands. Beerstecher [223] studied the estrogens excreted in the urine of vitamin E–deficient female rats and found their values to decrease abruptly at about

218. Krakower, C., and Axtmayer, J. H.: Effect of Alpha-Tocopherol on Lesions of Skeletal Muscles in Rats on Vitamin A-Deficient Diets, Proc. Soc. Exper. Biol. & Med. **45**:583-586 (Nov.) 1940.

219. Beard, H. H., and Pizzolato, P.: The Effect of Parenteral Injection of Crystalline Vitamins upon the Concentration of Muscle Creatine in the Rat, J. Am. Dietet. A. **17**:446-449 (May) 1941.

220. Holmes, A. D., and Pigott, M. G.: The Effect of Thiamin Hydrochloride on the Muscular Dystrophy of Avitaminosis-E, Am. J. Physiol. **132**:211-214 (Feb.) 1941.

221. Mackenzie, C. G., and McCollum, E. V.: Muscular Dystrophy in the Absence of Testicular Degeneration in Vitamin E Deficiency, Proc. Soc. Exper. Biol. & Med. **47**:148-152 (May) 1941.

222. Biddulph, C., and Meyer, R. K.: The Influence of Vitamin E-Deficiency on the Endocrine Glands of Rats, Particularly on the Gonadotropic Hormone Content of the Pituitary Gland, Am. J. Physiol. **132**:259-271 (Feb.) 1941.

223. Beerstecher, E., Jr.: Estrogens in Urine of Normal and Vitamin E Depleted Rats, Endocrinology **28**:344 (Feb.) 1941.

the eighteenth day of deprivation. He found a rather significant correlation between the decrease in estrogens and the decrease in weight of the resorbing fetuses. Adamstone [224] found that vitamin E hastened the effect of testosterone propionate in reviving the secondary sex characteristics of caponized male fowls and concluded that a certain quantity of vitamin E in the diet is necessary for the most effective utilization of androgens.

Mackenzie, Mackenzie and McCollum [225] observed that the administration of cod liver oil rendered alpha tocopherol ineffective in the prevention of muscular dystrophy in rabbits. The cause of this is obscure, but the authors have offered three possible explanations: 1. Vitamin E may be destroyed by cod liver oil after ingestion. 2. Cod liver oil may exert some sort of toxic action on the muscles. 3. The destructive action of cod liver oil may be prevented by vitamin E, by virtue of its activity as either a vitamin or an antioxidant.

Adamstone [226] fed chicks on ferric chloride–treated rations supplemented by halibut liver oil and observed the development of a type of anemia characterized by marked erythrophagocytosis. When the halibut liver oil was replaced by cod or salmon liver oil, this reaction did not appear; it was likewise prevented by the addition of vitamin E to the diet. The cause of this phenomenon is not clear, but it is suggested that treatment of the food destroyed some substance essential to the erythrocytes, a substance which may be available in cod and salmon liver oils.

Clinical Use.—The various claims and counterclaims for the use of vitamin E in neuromyogenic disturbances are at such variance as to make critical analysis almost impossible. Save for the studies of Wechsler,[227] favorable reports [228] have been based on small series of

224. Adamstone, F. B.: Relation of Vitamin E to the Effectiveness of Testosterone Injected into Caponized Male Fowls, Arch. Path. **31**:706-710 (June) 1941.

225. Mackenzie, C. G.; Mackenzie, J. B., and McCollum, E. V.: Uncomplicated Vitamin E Deficiency in the Rabbit and Its Relation to the Toxicity of Cod Liver Oil, J. Nutrition **21**:225-234 (March) 1941.

226. Adamstone, F. B.: Erythrophagocytosis in Chicks Reared on a Vitamin E-Deficient Ration Supplemented with Halibut Liver Oil, Arch. Path. **31**:613-621 (May) 1941.

227. Wechsler, I. S.: The Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Tocopherols), Am. J. M. Sc. **200**:765-778 (Dec.) 1940.

228. Weinberg, M. H., and Knoll, A. F.: Beneficial Effect of Vitamin E on Amyotrophic Lateral Sclerosis Syndrome: Report of a Case in Which This Syndrome Was Precipitated by Sulfathiazole, M. Rec. **152**:447-448 (Dec. 18) 1940. Stone, S.: Vitamin E in the Treatment of Muscle Disorders of Infancy and Childhood, J. Pediat. **18**:310-316 (March) 1941. Slaughter, R. F., and Cleckley, H.: The Treatment of Intrinsic Cord Disease with Vitamin E, J. M. A. Georgia **30**:106-108 (March) 1941. de Gutiérrez-Mahoney, W.: Neural Myatrophy and Vitamin E, South. M. J. **34**:389-394 (April) 1941.

cases, in which there was little chance for adequate control. In discussing a paper by Rhoads,[229] Stone stated that he observed improvement in 10 of 20 patients who had muscular dystrophy and were treated with vitamin E. This again is at variance with Wechsler's [227] observations, since Wechsler was unable to note any improvement in this type of disturbance after administration of the vitamin. It is difficult to reconcile these reports with those of Doyle and Merritt,[230] as well as with those of other investigators,[231] who were unable to observe any objective improvement among patients in relatively large series of cases. Fleischmann [232] treated 3 patients with alpha tocopherol, with completely negative results and with no effect on the creatine-creatinine excretion. The latter observation led him to believe that there is some fundamental difference between the neuromyopathies of human beings and those of vitamin E–deficient animals. On the basis of determinations of serum tocopherol Wechsler and associates [233] could not discover any difference in values obtained for their patients and those of normal controls (0.59 to 1.62 mg. per hundred cubic centimeters). After the administration of tocopherol, there was a uniform increase in these values, but there was no relation between this increase and the clinical improvement. These observations led them to conclude that these "figures . . . do not point to a simple deficiency in amyotrophic lateral sclerosis." A good summary of this entire subject has appeared in editorial form in the *Lancet*.[234]

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229. Rhoads, C. P.: Deficiency Diseases: Their Diagnosis and Treatment, New England J. Med. **224**:493-497 (March 20) 1941.

230. Doyle, A. M., and Merritt, H. H.: Vitamin Therapy of Diseases of Neuromuscular Apparatus, Arch. Neurol. & Psychiat. **45**:672-679 (April) 1941.

231. McBryde, A., and Baker, L. D.: Vitamin Therapy in Progressive Muscular Dystrophy: Vitamin B_6, Other Factors of the B Complex, and Vitamin E, J. Pediat. **18**:727-731 (June) 1941. Worster-Drought, C., and Shafar, J.: Motor Neuron Degeneration Treated with Vitamin E., Lancet **2**:209-212 (Aug. 23) 1941. Harris, M. M.: Negative Therapeutic and Metabolic Effects of Synthetic Alpha-Tocopherol (Vitamin E) in Muscular Dystrophy, Am. J. M. Sc. **202**:258-264 (Aug.) 1941. Ferrebee, J. W.; Klingman, W. O., and Frantz, A. M.: Vitamin E and B_6: Clinical Experience in the Treatment of Muscular Dystrophy and Amyotrophic Lateral Sclerosis, J. A. M. A. **116**:1895-1896 (April 26) 1941. Denker, P. G., and Scheinman, L.: Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Alpha-Tocopherol), ibid. **116**:1893-1895 (April 26) 1941. Fitzgerald, G., and McArdle, B.: Vitamins E and B_6 in the Treatment of Muscular Dystrophy and Motor Neurone Disease, Brain **64**:19-42 (March) 1941.

232. Fleischmann, W.: Creatine-Creatinine Excretion in Neuromuscular Diseases Treated with Alpha-Tocopherol and with Testosterone, Proc. Soc. Exper. Biol. & Med. **46**:94-97 (Jan.) 1941.

233. Wechsler, I. S.; Mayer, G. G., and Sobotka, H.: Tocopherol Level in Serum of Normals and Patients with Amyotrophic Lateral Sclerosis, Proc. Soc. Exper. Biol. & Med. **47**:152-156 (May) 1941.

234. Vitamin E Falls from Grace, editorial, Lancet **2**:219-220 (Aug. 23) 1941.

Lubin and Waltman [235] published results of a study of the role of vitamin E in habitual abortion. Among their 7 patients the administration of alpha tocopherol was followed by successful parturition in 5. The authors were properly conservative in their conclusions but expressed the belief that their results were sufficiently encouraging to stimulate further investigation. Adamstone [236] observed a disturbance of cholesterol metabolism in vitamin E–deficient chicks; since there may be a similar disturbance in cases of habitual abortion, he suggested that there may be a definite role for vitamin E in cholesterol metabolism.

VITAMIN K

Chemical and Physiologic Properties.—The compound 2-methyl-1,4-naphthoquinone is one of the most active synthetic antihemorrhagic compounds known. Because of the wide usefulness of this compound in clinical medicine, the Council on Pharmacy and Chemistry of the American Medical Association,[237] on the recommendation of the Committee on Nomenclature, authorized "menadione" as the nonproprietary name for this substance.

Many of the advances in the chemistry of vitamin K have been made in the study of various quinone derivatives,[238] and excellent reviews [239] of these investigations have appeared. Naturally, considerable effort also has been made in the hope of obtaining knowledge concerning the activity and structure of vitamin K. Fieser and his associates [240] studied some seventy-nine compounds with antihemorrhagic activity in an effort to obtain some knowledge on this point. They found that antihemor-

235. Lubin, S., and Waltman, R.: The Use of Synthetic Vitamin E in the Treatment of Abortion, Am. J. Obst. & Gynec. **41**:960-970 (June) 1941.

236. Adamstone, F. B.: Cholesterol Content of Brain in Nutritional Encephalomalacia of Vitamin E-Deficient Chicks, Arch. Path. **31**:711-716 (June) 1941.

237. Menadione, Nonproprietary Term for the Substance 2-Methyl-1, 4-Naphthoquinone, report of the Council on Pharmacy and Chemistry, J. A. M. A. **116**: 1054 (March 15) 1941.

238. (*a*) Lee, J.; Solmssen, U. V.; Steyermark, A., and Foster, R. H. K.: Antihemorrhagic Activity of Tetra Sodium 2-Methyl-1, 4-Naphthohydroquinone Diphosphoric Acid Ester and Other Naphthoquinone Derivatives, Proc. Soc. Exper. Biol. & Med. **45**:407-412 (Oct.) 1940. (*b*) Foster, R. H. K., with the technical assistance of Clark, H. H.: Pharmacological Observations on Tetra-Sodium-2-Methyl-1, 4-Naphthohydroquinone Diphosphoric Acid Ester, ibid. **45**:412-415 (Oct.) 1940. (*c*) Almquist, H. J., and Klose, A. A.: Comparative Activities of Certain Antihemorrhagic Compounds, ibid. **45**:55-59 (Oct.) 1940. (*d*) Martin, G. J., and Lischer, C. F.: Polyhydroxyanthraquinones Affecting Coagulation Time in Vitamin K Deficiency, J. Biol. Chem. **137**:169-171 (Jan.) 1941.

239. Karrer, P.: Das antihämorrhagische Vitamin K, Schweiz. med. Wchnschr. **70**:537-541 (June 15) 1940. Doisy, E. A.; Binkley, S. B., and Thayer, S. A.: Vitamin K, Chem. Rev. **28**:477-517 (June) 1941.

240. Fieser, L. F.; Tishler, M., and Sampson, W. L.: Vitamin K Activity and Structure, J. Biol. Chem. **137**:659-692 (Feb.) 1941.

rhagic activity of any biologically significant magnitude is found only in the 1,4-naphthoquinone series or among compounds which are convertible into such quinones. Considerable specificity is evident in the series which embraces vitamin K_1 and vitamin K_2. These investigators reported that the high potency of menadione is almost completely wiped out when the methyl group is replaced by an ethyl or a propyl group or when a methyl group is introduced at any of the four positions in the benzenoid ring. It is interesting that the antihemorrhagic activity which was observed in a considerable number of the compounds tested by these authors seemed to be attributable not to the function of the actual substance administered but to its conversion in the animal body to a vitamin K type principle in the course of the action. McCawley and Gurchot [241] reported that the degree of activity of vitamin K is roughly proportional to the length of the side chain and to the degree to which it approximates the characteristic structure of natural vitamins. This group of authors believed that vitamin K is a reversible oxidation-reduction catalyst, the hydroquinone form of which is readily oxidized by molecular oxygen. It is suggested that the reversible character of the vitamin may be used to explain the fact that small quantities are effective clinically.

Javert and Macri [242] emphasized that excessive amounts of mineral oil administered with meals may prevent proper absorption of vitamin K, with a resulting deficiency of prothrombin in the circulating blood. Morse and Schmidt [243] pointed out that both phthiocol (2-methyl-3-hydroxy-1,4-naphthoquinone) and menadione are absorbed from the intestinal tracts of rats with bile fistulas and that desoxycholic acid is not necessary to insure the absorption of these compounds. It has been reported that a synthetic compound possessing vitamin K activity produces vitamin K stores in newly hatched chicks when injected into eggs prior to incubation. The injected vitamin apparently protects against the rapid and extreme decrease in prothrombin which occurs when chicks are placed on a vitamin K–free diet.[244] McElroy and Goss [245] have demonstrated that vitamin K is not a dietary essential for

241. McCawley, E. L., and Gurchot, C.: A Mechanism of Action for Vitamin K, Univ. California Publ., Pharmacol. **1**:325-338, 1940.

242. Javert, C. T., and Macri, C.: Prothrombin Concentration and Mineral Oil, Am. J. Obst. & Gynec. **42**:409-414 (Sept.) 1941.

243. Morse, L. M., and Schmidt, C. L. A.: Absorption of 2-Methyl-1, 4-Naphthoquinone Phthiocol by Bile Fistula Rats, Proc. Soc. Exper. Biol. & Med. **46**:415-416 (March) 1941.

244. Tidrick, R. T.; Stamler, F. W.; Joyce, F. T., and Warner, E. D.: Vitamin K Storage and Prothrombin Levels in Chicks Obtained from Injected Eggs, Proc. Soc. Exper. Biol. & Med. **47**:438-440 (June) 1941.

245. McElroy, L. W., and Goss, H.: A Quantitative Study of Vitamins in the Rumen Contents of Sheep and Cows Fed Vitamin-Low Diets: I. Riboflavin and Vitamin K, J. Nutrition **20**:527-540 (Dec.) 1940.

the cow and that the rumen of the experimental animal is a good source of vitamin K. It has also been found [246] that vitamin K and antihemorrhagic compounds in general are effective in promoting the growth of certain bacteria. Almquist and Mecchi [247] observed that menadione, pure vitamin K_1 and other quinone derivatives do not prevent erosion of the lining of the gizzard of chicks.

In reasonable clinical doses no serious untoward reaction has yet been observed among human beings after the administration of either natural or synthetic compounds possessing vitamin K activity. Toxic effects have been noted among animals, however.[248] Shimkin,[248a] in a study of the acute and chronic toxic effects of six naphthoquinone compounds of vitamin K activity, observed that the compounds in high doses are respiratory depressants and produce acute vascular congestion which is sufficient to cause hemorrhagic extravasation into the renal tubules and within the liver. Loss of weight, anemia or morphologic changes were not observed in mice which were given subcutaneous injections of 4 to 18 mg. of menadione daily for three to six weeks.

The wide interest in vitamin K and the associated naphthoquinones has given rise to the need for convenient and accurate methods for their estimation. A step in this direction was made by Trenner and Bacher,[249] who described a method by which many quinone-like substances may be assayed. It is a quantitative reduction-oxidation method. They encountered no interference when other fat-soluble vitamins, such as A, B or E, were used. Excellent critical reviews of biologic methods for measuring vitamin K were given by Ansbacher [250] and Almquist.[251]

Prothrombin.—Recently, a method has been described [252] by which prothrombin can be produced in a fairly pure form, and in several other

246. Woolley, D. W., and McCarter, J. R.: Antihemorrhagic Compounds as Growth Factors for Johne's Bacillus, Proc. Soc. Exper. Biol. & Med. **45**:357-360 (Oct.) 1940.

247. Almquist, H. J., and Mecchi, E.: Influence of Bile Acids, Vitamin K and Cinchophen on Erosions of the Chick Gizzard Lining, Proc. Soc. Exper. Biol. & Med. **46**:168-172 (Jan.) 1941.

248. (*a*) Shimkin, M. B.: Toxicity of Naphthoquinones with Vitamin K Activity in Mice, J. Pharmacol. & Exper. Therap. **71**:210-214 (March) 1941. (*b*) Foster.[248b]

249. Trenner, N. R., and Bacher, F. A.: A Quantitative Reduction-Oxidation Method for the Estimation of Vitamin K_1 and Associated Quinones and Naphthoquinones, J. Biol. Chem. **137**:745-755 (Feb.) 1941.

250. Ansbacher, S.: The Bioassay of Vitamin K, J. Nutrition **21**:1-12 (Jan.) 1941.

251. Almquist, H. J.: Vitamin K, Physiol. Rev. **21**:194-216 (Jan.)1941.

252. Seegers, W. H., and Smith, H. P.: The Purification of Prothrombin, J. Biol. Chem. **140**:677-678 (Aug.) 1941.

studies [253] the physical and physiologic properties of this substance have been considered. It has been suggested,[254] also, that prothrombin is destroyed in the lung. These data have not yet been confirmed. Cullen and his associates [255] found that chloroform anesthesia in the human being produces a decrease in the plasma prothrombin level, whereas ether and cyclopropane anesthesia do not. They assumed that the decrease in the level of plasma prothrombin which occurs after surgical operation on patients suffering from obstructive jaundice or biliary fistula evidently is due essentially to factors other than the anesthetic agent itself.

Methods for the measurement of prothrombin now in general use are those described by Quick and his associates and by Warner and his co-workers. Herbert [256] described a modification of the latter method, and Souter and Kark [257] suggested that the Quick prothrombin test can be simplified by the use of stable thromboplastin.

Clinical Use of Vitamin K.—Among Adults: There has appeared during the past year a large number of articles which support the evidence presented in last year's review that vitamin K in its natural form or in one of its many synthetic forms is capable of controlling deficiency of prothrombin which occurs in man as the result of deficiency of vitamin K. The entire problem has been fully discussed in recent monographs by Snell and one of us (H. R. B.),[258] Brinkhous [259] and Bay.[260] Several brief discussions of the general problem also have appeared.[261]

253. Ferguson, J. H.: Stability of Prothrombin in the Presence of Thrombin, Proc. Soc. Exper. Biol. & Med. **46**:80-83 (Jan.) 1941. Orr, W. F., Jr., and Moore, D. H.: Studies on Identity of Prothrombin, ibid. **46**:357-360 (Feb.) 1941. Shafiroff, B. G. P.; Doubilet, H., and Tui, C. O.: Effect of Intramuscular Injection of Sodium Citrate on the Prothrombin Time of the Blood, ibid. **46**:136-139 (Jan.) 1941.

254. Lord, J. W., Jr.; Andrus, W. D., and Moore, R. A.: Metabolism of Vitamin K, and Role of the Liver in Production of Prothrombin in Animals, Arch. Surg. **41**:585-595 (Sept.) 1940.

255. Cullen, S. Z.; Ziffren, S. Z.; Gibson, R. V., and Smith, H. T.: Anesthesia and Liver Injury with Special References to Plasma Prothrombin Levels, J. A. M. A. **115**:991-994 (Sept. 21) 1940.

256. Herbert, F. K.: The Estimation of Prothrombin in Human Plasma, Biochem. J. **34**:1554-1568 (Dec.) 1940.

257. Souter, A. W., and Kark, R.: Quick's Prothrombin Test Simplified by the Use of a Stable Thromboplastin, Am. J. M. Sc. **200**:603-607 (Nov.) 1940.

258. Butt, H. R., and Snell, A. M.: Vitamin K, Philadelphia, W. B. Saunders Company, 1941.

259. Brinkhous, K. M.: Plasma Prothrombin, Vitamin K, Medicine **19**:329-416 (Sept.) 1940.

260. Bay, R.: Higado-prothrombina-vitamin K (estudio experimental y clinico), Bol. Inst. de clín. quir. **17**:139-231 (Feb.-March) 1941.

261. Kark, R., and Souter, A. W.: Hypoprothrombinaemia and Avitaminosis-K in Man, Brit. M. J. **2**:190-194 (Aug. 9) 1941. Smith, H. P., and Owen, C. A.:

(Footnote continued on next page)

Menadione continues to be much favored in the treatment of deficiency of prothrombin. Both the oral and the intravenous form of administration of this compound in most cases have proved to be effective in controlling hypoprothrombinemia.[262] Stewart [262a] observed that the effectiveness of menadione taken by mouth is increased by the taking of desoxycholic acid or bile salts, even in the absence of jaundice. Moreover, this author did not observe any evidence of toxicity, even when as much as 20 mg. of menadione was given intravenously in one dose. Others [262c] confirmed the fact, already established, that the intravenous administration of menadione results in a rapid decrease in an elevated prothrombin clotting time.

Again, the water-soluble compound 4-amino-2-methyl-1-naphthol hydrochloride has proved to be just as effective when administered intravenously as the derivative of menadione.[263] A definite response to the intravenous administration of this compound was noted within three quarters of an hour to one and a half hours after administration.[263d] No toxic effects were observed after doses ranging to as high as 6 mg.

Vitamin K.: Its Use in Patients with Obstructive Jaundice or with Biliary Fistulas, Rev. Gastroenterol. **7**:520-528 (Nov.-Dec.) 1940. Hicks, J. D.: A Review of the Literature Concerning Haemorrhage in Obstructive Jaundice: The Significance of Prothrombin and of Vitamin K Therapy, M. J. Australia **1**:46-51 (Jan. 11) 1941. Reid, J.: Prothrombin Deficiency in Disease of the Liver and Bile Passages and Its Treatment with Synthetic Vitamin K, Brit. M. J. **1**:4189-4194 (April 19) 1941. Cheney, G.: The Clinical Value of Vitamin K, J. A. M. A. **115**:1082-1087 (Sept. 28) 1940. Freeman, S., and Grodins, F. S.: Recent Studies of the Factors Involved in the Coagulation of Blood, Including a Review of Vitamin K, Internat. Abstr. Surg. **72**:417-427, 1941; in Surg., Gynec. & Obst., May 1941.

262. (*a*) Stewart, J. D.: Oral and Parenteral Use of Synthetic Vitamin K-Active Substances in Hypoprothrombinemia, Surgery **9**:212-219 (Feb.) 1941. (*b*) Norcross, J. W., and McFarland, M. D.: Intravenous Use of 2-Methyl-1,4-Naphthoquinone in Hypoprothrombinemia: Clinical Observations, J. A. M. A. **115**:2156-2161 (Dec. 21) 1940. (*c*) Tocantins, L. M., and Jones, H. W.: Hypoprothrombinemia: Effect of Peroral and Parenteral Administration of a Synthetic Vitamin K Substitute (2-Methyl-1,4-Naphthoquinone), Ann. Surg. **113**:276-283 (Feb.) 1941. (*d*) Anderson, E. R.; Karabin, J. E.; Udesky, H. L., and Seed, L.: The Oral Administration of Synthetic Vitamin K (2-Methyl-1,4-Naphthoquinone), Surgery **9**:361-371 (March) 1941.

263. (*a*) Sharp, E. A.; Konder Heide, E. C., and Good, W. H.: Vitamin K Activity of 2-Methyl-1,4-Naphthoquinone and 4-Amino-2-Methyl-1-Naphthol in Hypoprothrombinemia, J. Lab. & Clin. Med. **26**:818-822 (Feb.) 1941. (*b*) Olwin, J. H.: The Intravenous Use of Vitamin K, J. A. M. A. **117**:432-435 (Aug. 9) 1941. (*c*) Emmett, A. D.; Kamm, O., and Sharp, E. A.: The Vitamin K Activity of 4-Amino-2-Methyl-1-Naphthol and 4-Amino-3-Methyl-1-Naphthol, J. Biol. Chem. **133**:285-286 (March) 1940. (*d*) Anderson, E. R.; Karabin, J. E.; Udesky, H., and Seed, L.: Parenteral Administration of a Water-Soluble Compound with Vitamin K Activity: 4-Amino-2-Methyl-1-Naphthol Hydrochloride, Arch. Surg. **41**:1244-1250 (Nov.) 1940.

had been administered. It was also suggested by Olwin that 4-amino-2-methyl-1-naphthol hydrochloride, 2-methyl-1-,4-naphthohydroquinone-3-sodium sulfonate, 2-methyl-1,4-dihydroxynaphthalene diphosphoric acid ester tetra sodium salt all may be of definite practical use.[263b]

In almost all the clinical studies just mentioned, the synthetic quinone derivatives with vitamin K activity were employed in the treatment of hypoprothrombinemia resulting from obstructive jaundice from one cause or another. In such a condition its clinical use is established without doubt. Some investigators [264] have recently expressed the opinion that the change effected in a particular level of prothrombin by the administration of vitamin K may provide some index as to the nature of the disease being treated, with particular reference to intrahepatic and extrahepatic jaundice. Data [265] now at hand do not unequivocally establish this fact. Almost all investigators,[266] however, agree that deficiency of prothrombin resulting from severe primary hepatic injury is not controlled by the administration of vitamin K in any amount. Some investigators have contended that there is a correlation between the Quick hippuric acid test for hepatic function and the level of prothrombin in the circulating blood. Recent work [267] does not substantiate this view.

The suggestion that deficiency of prothrombin can occur in various intestinal disturbances continues to be supported.[268] Apparently, such a deficiency is not uncommon in sprue and various forms of idiopathic steatorrhea. Others,[269] in a study of values for prothrombin among patients suffering from pellagra and associated nutritional deficiency states, have observed that deficiency of vitamin K was not common in

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264. Allen, J. G., and Julian, O. C.: Response of Plasma Prothrombin to Vitamin K Substitute Therapy in Cases of Hepatic Disease, Arch. Surg. **41**:1363-1365 (Dec.) 1940. Andrus, W. DeW.: The Newer Knowledge of Vitamin K, Bull. New York Acad. Med. **17**:116-134 (Feb.) 1941.

265. Butt, H. R.: Unpublished data.

266. (*a*) Lucia, S. P., and Aggeler, P. M.: The Influence of Liver Damage on the Plasma Prothrombin Concentration and the Response to Vitamin K, Am. J. M. Sc. **201**:326-340 (March) 1941. (*b*) Kark, R.; White, F. W.; Souter, A. W., and Deutsch, E.: Blood Prothrombin Levels and Hippuric Acid Excretion Liver Function Test in Liver Disease, Proc. Soc. Exper. Biol. & Med. **46**:424-426 (March) 1941. (*c*) Butt and Snell.[258] (*d*) Brinkhaus.[259] (*e*) Butt.[265]

267. Footnote 266 *a* and *b*.

268. Kark, R.; Souter, A. W., and Hayward, J. C.: A Haemorrhagic Diathesis in Idiopathic Steatorrhoea: Observations on Its Association with Vitamin K Deficiency, Quart. J. Med. **9**:247-261 (Oct.) 1940. Allen, J. G.: The Comparative Prothrombin Responses to Vitamin K and Several of Its Substitutes in a Case of Nontropical Sprue, New England J. Med. **224**:195-197 (Jan. 30) 1941. Sharp, Konder Heide and Good.[263a]

269. Warner, E. D.; Spies, T. D., and Owen, C. A.: Hypoprothrombinemia and Vitamin K in Nutritional Deficiency States, South. M. J. **34**:161-163 (Feb.) 1941.

cases of these types. They did observe, however, that prolonged diarrhea at times results in a serious deficiency of this vitamin. Many chronically debilitated patients have a moderate deficiency of prothrombin which apparently is due to causes other than deficiency of vitamin K, since administration of vitamin K to these patients does not elevate the level of prothrombin. Chute [270] claimed that vitamin K was of value in the control of abnormal bleeding occurring in a patient suffering from a renal stone who underwent a surgical procedure and in whom fever later developed. Others [271] found that vitamin K was of no effect in the control of pulmonary hemorrhage associated with tuberculosis.

Among Infants: During the past year numerous reports have appeared on the effect of compounds possessing vitamin K activity on the prothrombin level of the newborn infant. The suggestion made more than a year ago by Waddell and Guerry that no surgical procedure be performed on any newborn infant without the prophylactic administration of vitamin K has proved to be eminently sensible.

Several groups of investigators [272] have reestablished the fact that the normal increase in the prothrombin clotting time of the newborn infant will be prevented by administration of vitamin K to the mother prior to delivery and to the newborn infant. Again, it has been emphasized [273] that the intramuscular administration of blood to the newborn

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270. Chute, R.: The Value of Vitamin K in the Treatment of Abnormal Bleeding, New England J. Med. **224**:360-361 (Feb. 27) 1941.

271. Kaplan, R. H.: Use of Vitamin K in the Hemoptysis of Pulmonary Tuberculosis, M. Bull. Vet. Admin. **18**:48 (July) 1941. Harrell, C. L., and Ray, A. C.: Pulmonary Hemorrhage in Tuberculosis and Thyloquinone or Vitamin K, Virginia M. Monthly **68**:451-456 (Aug.) 1941.

272. (*a*) Lawson, R. B.: Treatment of Hypoprothrombinemia (Hemorrhagic Disease) of the Newborn Infant, J. Pediat. **18**:224-234 (Feb.) 1941. (*b*) Bruchsaler, F. S.: Vitamin K and the Prenatal and Postnatal Prevention of Hemorrhagic Disease in Newborn Infants, ibid. **18**:317-320 (March) 1941. (*c*) Willumsen, H. C.; Stadler, H. E., and Owen, C. A.: Comparative Effect of Vitamin K and Whole Blood on Prothrombin Deficiency of Newborn Infant, Proc. Soc. Exper. Biol. & Med. **47**:116-121 (May) 1941. (*d*) Leidenheimer, H., Jr., and Albritton, A. S.: Studies on the Bleeding Tendency and Vitamin K Therapy in Newborn Children, New Orleans M. & S. J. **93**:464-470 (March) 1941. (*e*) Mull, J. W.; Bill, A. H., and Skowronska, H.: Effect on the Newborn of Vitamin K Administered to Mothers in Labor, J. Lab. & Clin. Med. **26**:1305-1309 (May) 1941. (*f*) Bohlender, G. P.; Rosenbaum, W. M., and Sage, E. C.: Antepartum Use of Vitamin K in the Prevention of Prothrombin Deficiency in the Newborn, J. A. M. A. **116**:1763-1766 (April 19) 1941. (*g*) Snelling, C. E., and Nelsen, W.: Vitamin K in Hemorrhagic Disease of the Newborn Infant, J. Pediat. **17**:615-620 (Nov.) 1940. (*h*) Valentine, E. H.; Reinhold, J. G., and Schneider, E.: The Effectiveness of Prenatal Administration of 2-Methyl-1,4-Naphthoquinone in Maintaining Normal Prothrombin Levels in Infants, Am. J. M. Sc. **202**:359-364 (Sept.) 1941.

273. Footnote 272 *a* and *b*.

infant is of no advantage in the prophylactic treatment of deficiency of prothrombin. It has been demonstrated [274] that not only is menadione effective in the treatment of the newborn infant but that 2-methyl-1,4-dihydroxynaphthalene diphosphoric acid ester tetra sodium salt also is effective. Others [275] have pointed out that there is no relation between the mother's diet and the postpartum level of prothrombin in the newborn infant. Apparently, a completely adequate diet, as it is understood today, for the pregnant woman is not sufficient to protect the child from the potential danger of hemorrhage. Javert and Macri [276] observed that in normal pregnancy the prothrombin level was 70 per cent or less among 15 per cent of 200 patients. This observation is not in keeping with those made in other reports. In an excellent study Sells and his associates [277] reported that the vitamin K requirement of newborn infants is extremely low. Approximately 1 microgram of synthetic vitamin K is a sufficient daily amount. They suggested that colostrum contains enough free vitamin K to meet this minimal requirement. This work has not yet been confirmed. The successful treatment of erythroblastosis in icterus gravis neonatorum with vitamin K has been reported.[278] For a review of the general subject the reader is referred to two papers.[279]

Vitamin K and its analogues have been successfully administered orally, intramuscularly and intravenously. Recently, it has been reported that it may be possible to administer this compound by inunction. It was first reported by DeBeer and his associates [280] that a synthetic compound possessing vitamin K activity dissolved in a warm mixture of hydrous wool fat and liquid petrolatum could be rubbed underneath the wing of a vitamin K–deficient chick, with resulting effect

274. McCready, R. L.; Callahan, E. T., and Grandin, D. J.: Parenteral Vitamin K Therapy in Ante-Partum Women and Its Effects on the Infants' Prothrombin Levels: A Preliminary Report, Am. J. Obst. & Gynec. **42**:398-404 (Sept.) 1941.

275. Astrowe, P. S.; Palmerton, E. S., and Henderson, V.: Clinical Studies with Vitamin K in Newborn Infants, J. Pediat. **18**:507-515 (April) 1941.

276. Javert, C. T., and Macri, C.: Prothrombin Concentration in Normal Pregnancy, Am. J. Obst. & Gynec. **42**:415-419 (Sept.) 1941.

277. Sells, R. L.; Walker, S. A., and Owen, C. A.: Vitamin K Requirement of the Newborn Infant, Proc. Soc. Exper. Biol. & Med. **47**:441-445 (June) 1941.

278. Mayman, E. W.: Erythroblastosis in Icterus Gravis Neonatorum Successfully Treated with Vitamin K, J. Pediat. **17**:806-808 (Dec.) 1940.

279. Grossman, A. M.: Practical Therapy with Vitamin K.: A Simple Reclassification of Hemorrhagic Diseases Due to a Deficiency of Blood Prothrombin, M. Ann. District of Columbia **10**:218-225 (June) 1941. Savage, H.: The Development of Vitamin K and Its Clinical Uses in the Neonatal Period, Arch. Dis. Childhood **16**:67-70 (March) 1941.

280. DeBeer, E. J.; Drektar, L., and Flusser, B.: Routes of Administration of Materials Capable of Acting as Vitamin K, Proc. Soc. Exper. Biol. & Med. **46**:535-537 (April) 1941.

on the diminished level of prothrombin. Recently, this experimental knowledge has been applied clinically by Russell and Page.[281] These authors embodied 1 per cent menadione in a specially prepared base. Newborn infants were given 10 mg. of this mixture, applied to the skin of the back, on the first and second days of life. The prothrombin clotting time showed a steady decrease and was within normal limits by the fifth day. No newborn infants treated in this manner exhibited the so-called physiologic deficiency of prothrombin. These authors also described a new method for micromeasurement of prothrombin in which Russell's viper venom was employed. Other authors[273] also have reported microtests for prothrombin.

Two rather extensive studies[282] on this general problem warrant some discussion. Beck and co-workers[282a] reported that only 5, or 0.5 per cent, of 1,022 infants whose mothers had received vitamin K prior to delivery showed any evidence of hemorrhage, in contrast to 21, or 2 per cent, of 1,037 infants (controls) whose mothers had not received vitamin K prior to delivery. In this series of 2,059 cases, in which alternate mothers received vitamin K, it appears that the administration of vitamin K prior to delivery reduced the incidence of hemorrhage in the newborn infant by approximately 75 per cent. These authors gave 2 mg. of menadione by mouth to the mother one-half hour to forty-four hours before delivery. Hellman, Shettles and Eastman[282b] have continued their extensive study of the problem and recently reviewed one year's experience, which should be read by every one interested in prenatal care. These authors have already demonstrated that the plasma level of prothrombin in the newborn infant can be increased by administering vitamin K to the mother, even if it is given as late as four hours before delivery. They found that although the feeding of vitamin K to a baby after birth increased the concentration of prothrombin, the levels of prothrombin in these instances were not so high as those achieved by antepartum administration of the vitamin to the mother. The evidence which they had at hand suggested that many instances of cerebral hemorrhage occurring during birth, with minimal birth trauma, are precipitated by small hemorrhages which endure for a number of days. For this reason, these authors expressed the belief that the lives of some of the infants might have been saved had their blood at birth exhibited better prop-

281. Russell, H. K., and Page, R. C.: Effect of Topical Application of 2-Methyl-1,4-Naphthoquinone (Synthetic Vitamin K Analogue) on the Prothrombin Level of Newborn Infants, with Reference to a Simplified Microprothrombin Test, Am. J. M. Sc. **202**:355-359 (Sept.) 1941.

282. (*a*) Beck, A. C.; Taylor, E. S., and Colburn, R. F.: Vitamin K Administered to the Mother During Labor as a Prophylaxis Against Hemorrhage in the Newborn Infant, Am. J. Obst. & Gynec. **41**:765-775 (May) 1941. (*b*) Hellman, L. M.; Shettles, L. B., and Eastman, N. J.: Vitamin K in Obstetrics: A Review of One Year's Experience, ibid. **40**:844-853 (Nov.) 1940.

erties of coagulation. Beginning on Sept. 1, 1939, every other patient in labor admitted to the obstetric service at the Johns Hopkins Hospital received vitamin K by mouth. Menadione in a single dose of 2 mg. was employed. By May 1, 1940, 384 mothers had received vitamin K in labor, whereas in the control series there were 392 patients. No specific effect was noted on postpartum hemorrhage after administration of vitamin K, and the weight of infants at discharge from the hospital in relation to the weight at birth was about the same in the two groups. The rate for stillbirths and neonatal mortality was 16 deaths, or 4.1 per cent, in the control series; in the series in which vitamin K had been used there were 6 deaths, or a mortality rate of 1.5 per cent. The infant death rate in the control series accordingly was two and seven-tenths times that of the series in which vitamin K had been administered. In studies of these infants at necropsy an interesting fact was noted: In only 1 of the 6 dead infants whose mothers had received vitamin K was hemorrhage demonstrable. This infant had been born by breech delivery, and necropsy disclosed subarachnoidal hemorrhage. In the control series, hemorrhage into one or another organ was demonstrable at necropsy in 9, or 56 per cent, of the 16 infants. In 3 cases extensive cerebral hemorrhage was present to account for the death of the infant. In a study of the retinas of 92 infants in the control group, hemorrhage was demonstrable in 29, or 32 per cent. Among the 75 infants whose mothers had received vitamin K, retinal hemorrhages were demonstrable in 12, or 16 per cent. Therefore, the frequency of retinal hemorrhage in the control group was twice that in the group of infants whose mothers had been treated prophylactically with vitamin K.

OTHER VITAMINS

During the past year many references have appeared in association with studies on vitamin H, or biotin.[283] Soon it was confirmed that

283. György, P.: The Curative Factor (Vitamin H) for Egg White Injury, with Particular Reference to Its Presence in Different Foodstuffs and in Yeast, J. Biol. Chem. **131**:733-744 (Dec.) 1939. Birch, T. W., and György, P.: Physicochemical Properties of the Factor (Vitamin H) Curative of Egg White Injury, ibid. **131**:761-766 (Dec.) 1939. György, P.; Kuhn, R., and Lederer, E.: Attempts to Isolate the Factor (Vitamin H) Curative of Egg White Injury, ibid. **131**:745-759 (Dec.) 1939. Eakin, R. E.; Snell, E. E., and Williams, R. J.: A Constituent of Raw Egg White Capable of Inactivating Biotin in Vitro, ibid. **136**:801-802 (Dec.) 1940. Hottle, G. A.; Lampen, J. O., and Pappenheimer, A. M., Jr.: Biotin as a Growth Factor for C203S Strain of Hemolytic Streptococcus Group A, ibid. **137**:457-458 (Jan.) 1941. McElroy, L. W., and Jukes, T. H.: Formation of the Anti Egg-White-Injury Factor (Biotin) in the Rumen of the Cow, Proc. Soc. Exper. Biol. & Med. **45**:296-297 (Oct.) 1940. György, P.; Melville, D. B.; Burk, D., and du Vigneaud, V.: The Possible Identity of Vitamin H with Biotin and Coenzyme R, Science **91**:243-245 (March 8) 1940.

vitamin H and biotin were identical,[284] and recently a method was described [285] for the isolation of a methyl ester of biotin from the liver. The analytic data agreed most closely with the empiric formula $C_{11}H_{18}O_3N_2S$.

Ansbacher,[286] during the past year, reported that paraaminobenzoic acid was a vitamin and that it possessed a chromotrichia factor for the rat and a growth-promoting factor for the chick. On the basis of his studies on rats and chicks, he concluded that this compound was one of the factors of the vitamin B complex. This acid also apparently modifies the formation of melanin [287] and when administered to man will result in the turning of gray hair to black.[288]

Vitamin L continues to be mentioned. It has been reported that subsistence on a dextrin diet leads to the production of vitamin L_2 by the intestinal yeasts.[289]

Recent experimental work has given rise to evidence that vitamin P may be of value in the control of vascular purpura. Rusznyák and Benkó [290] have shown that the administration of this factor will correct diminished capillary resistance both in guinea pigs and in rats. This is in agreement with the previous observations of Scarborough [291] concerning human beings. He wrote that two forms of subcutaneous hemorrhage may appear in deficiency states, due individually to deficiency of vitamins C and P. He expressed the belief that only vitamin P deficiency states are associated with a low capillary resistance. Rapaport and Klein [292] were able to duplicate this reduction of the

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284. du Vigneaud, V.; Melville, D. A.; György, P., and Rose, C. F.: On the Identity of Vitamin H with Biotin, Science **92**:62-63 (July 19) 1940. Porter, J. R., and Pelczar, M. J., Jr.: The Nutrition of Staphylococcus Aureus: The Influence of Biotin, Bios II_B and Vitamin H on the Growth of Several Strains, J. Bact. **41**:173-192 (Feb.) 1941. György, P.; Rose, C. S.; Hofmann, K.; Melville, D. B., and du Vigneaud, V.: A Further Note on the Identity of Vitamin H with Biotin, Science **92**:609 (Dec. 27) 1940.

285. du Vigneaud, V.; Hofmann, K.; Melville, D. B., and György, P.: Isolation of Biotin (Vitamin H) from Liver, J. Biol. Chem. **140**:643-651 (Aug.) 1941.

286. Ansbacher, S.: *p*-Aminobenzoic Acid, a Vitamin, Science **93**:164-165 (Feb. 14) 1941.

287. Martin, G. J.; Wisansky, W. A., and Ansbacher, S.: Para-Aminobenzoic Acid and Dopa Reaction, Proc. Soc. Exper. Biol. & Med. **47**:26-28 (May) 1941.

288. Sieve, B. F.: Clinical Achromotrichia, Science **94**:257-258 (Sept. 12) 1941.

289. Nakahara, W.; Inukai, F., and Ugami, S.: Vitamin L and Dextrin Diet, Science **93**:39-40 (Jan. 10) 1941.

290. Rusznyák, S., and Benkó, A.: Experimental Vitamin P Deficiency, Science **94**:25 (July 4) 1941.

291. Scarborough, H.: Deficiency of Vitamin C and Vitamin P in Man, Lancet **2**:644-647 (Nov. 23) 1940.

292. Rapaport, H. G., and Klein, S.: Vitamin P and Capillary Fragility, J. Pediat. **18**:321-327 (March) 1941.

capillary fragility in 100 allergic children. Other investigators have found vitamin P to be effective against allergic purpura,[293] infectious purpura,[293] purpura of measles,[294] purpura which occurs after arsenic therapy [295] and psoriasis.[296]

THE WASHINGTON YARDSTICK FOR NUTRITION

Of great significance for policy direction in current governmental activities designed to raise the nutritive quality of American diets was action taken by the Committee on Food and Nutrition and announced in May 1941 at the National Nutrition Conference for Defense. This committee was organized at the request of the government to advise on the scientific aspects of problems of nutrition in connection with national defense. Its early deliberations gave rise to the formulation of recommended daily allowances for those specific nutrients—protein, calcium, iron, vitamin A, thiamine, riboflavin, nicotinic acid and ascorbic acid—for which a human need has been clearly established. The recommended allowances are contained in the table. The recommendations were based on a critical appraisal of the literature and on opinions obtained from a considerable number of authorities on nutrition in various parts of the United States. They are believed to represent the combined judgment of American authorities on the amounts of the various nutritive essentials which it is desirable to include in practical diets. The term "recommended allowances" rather than "standards" or "optimal allowances" was used to avoid the implication of finality, and the urgent need for continued research on human needs was emphasized.

FORTIFICATION OF FOODS WITH VITAMINS AND MINERALS

Enriched flour, that is, plain white flour with thiamine, nicotinic acid and iron added in amounts such that the content of these nutrients approximates the content of them in whole wheat flour, appeared early in January 1941.[297] Enriched bread soon followed. This procedure was based on recommendations of the Committee on Food and Nutrition

293. Kugelmass, I. N.: Vitamin P in Vascular Purpura, J. A. M. A. **115**:519-520 (Aug. 17) 1940.

294. Miller, A. A.: Purpura in the Course of Measles: A Case Treated with Vitamin P, Brit. J. Child. Dis. **38**:1-14 (Jan.-March) 1941.

295. Gorrie, D. R.: Purpura Haemorrhagica After Arsenic Therapy Treated with Vitamin P, Lancet **1**:1005-1007 (June 1) 1940.

296. Goldfarb, A. E.: Treatment of Psoriasis with Lemon Citrin (Vitamin P), Citrin Lemonade and Ascorbic Acid, Arch. Dermat. & Syph. **43**:536-538 (March) 1941.

297. Vitamin-Enriched Flour Goes into Production, Science News Letter **39**: 83-84 (Feb. 8) 1941.

of the National Research Council.[298] It received the endorsements of the National Nutrition Conference for Defense, the Council on Foods and Nutrition and the House of Delegates of the American Medical Association. The general principle involved followed closely a policy adopted early in 1939 by the Council on Foods and Nutrition of the American Medical Association.[298c] The manufacture and distribution

Recommended Daily Allowances for Specific Nutrients Recommended by the Committee on Foods and Nutrition, National Research Council *

	Calories	Protein, Gm.	Calcium, Gm.	Iron, Mg.	Vitamin A, International Units †	Thiamine (Vitamin B_1), Mg. ‡	Riboflavin, Mg.	Nicotinic Acid, Mg.	Ascorbic Acid, Mg. §	Vitamin D, International Units
Man (70 Kg.)										
Moderately active	3,000	70	0.8	12	5,000	1.8	2.7	18	75	‖
Active	4,500	..	...	..	.....	2.3	3.3	23		
Sedentary	2,500	..	...	..	.....	1.5	2.2	15		
Woman (56 Kg.)										
Moderately active	2,500	60	0.8	12	5,000	1.5	2.2	15	70	‖
Active	3,000	..	...	..	.....	1.8	2.7	18		
Sedentary	2,100	..	...	..	.....	1.2	1.8	12		
Pregnant (in latter half of pregnancy)	2,500	85	1.5	15	6,000	1.8	2.5	18	100	400-800
Lactating	3,000	100	2.0	15	8,000	2.3	3.0	23	150	400-800
Children up to 12 years										
Under 1 year ¶	100/Kg.	3-4 Kg.	1.0	6	1,500	0.4	0.6	4	30	400-800
1 to 3 years #	1,200	40	1.0	7	2,000	0.6	0.9	6	35	‖
4 to 6 years	1,600	50	1.0	8	2,500	0.8	1.2	8	50	
7 to 9 years	2,000	60	1.0	10	3,500	1.0	1.5	10	60	
10 to 12 years	2,500	70	1.0	12	4,500	1.2	1.8	12	75	
Children over 12 years										
Girls, 13 to 15 years	2,800	80	1.3	15	5,000	1.4	2.0	14	80	‖
16 to 20 years	2,400	75	1.0	15	5,000	1.2	1.8	12	80	
Boys, 13 to 15 years	3,200	85	1.4	15	5,000	1.6	2.4	16	90	‖
16 to 20 years	3,800	100	1.4	15	6,000	2.0	3.0	20	100	

* Adapted from "Recommended Dietary Allowances," Nutrition Division, Federal Security Agency, Washington, D. C. These recommendations represent a tentative goal toward which to aim in planning practical dietaries and can be met by a good diet of natural foods. Such a diet will also provide other minerals and vitamins, the requirements for which are less well known.

† The requirements may be less of vitamin A as such is provided or greater if it is provided chiefly as the provitamin carotene.

‡ One milligram of thiamine hydrochloride equals 333 international units.

§ One milligram of ascorbic acid equals 20 international units.

‖ Vitamin D is undoubtedly necessary for older children and adults. When it is not available from sunshine it should be provided probably up to the minimum amount recommended for infants.

¶ The needs of infants increase from month to month. The amounts given are for infants about 6 to 8 months old. The amounts of protein and calcium may be less if they are derived from breast milk.

The allowances are based on the needs for the middle year in each group (2, 5, 8, etc.) and for moderate activity.

of enriched flour and bread have been proceeding rapidly. By the end of July 1941, 3,500,000,000 of the 10,500,000,000 pounds (1,600,-

298. (*a*) Wilder, R. M.: Nutrition Planning for the National Defense, War Med. **1**:143-157 (March) 1941; (*b*) Nutrition in the United States: A Program for the Present Emergency and the Future, Ann. Int. Med. **14**:2189-2198 (June) 1941; (*c*) Vitamin Restoration of Foods as Viewed by the Physician, Scient. Monthly **53**:295-302 (Oct.) 1941. (*d*) Williams, R. R.: Fortification and Restoration of Processed Foods, Indust. & Engin. Chem. (Indust. Ed.) **33**:718-720 (June 2) 1941.

000,000 of the 4,760,000,000 Kg.) of bakers' bread consumed annually in the United States was enriched bread [299] and more than 40 per cent of the flour for family use on the market was enriched.[300]

New evidence supporting the belief that enriched flour and bread represent products of superior nutritional value was presented by Elvehjem at the public hearings on bread held by the Food and Drug Administration during July and August 1941.[301] His analyses showed that whereas unenriched white flour contains little more than 10 per cent of the thiamine and nicotinic acid of the wheat from which it is made, it contains as much as 50 per cent of the riboflavin, the pyridoxine, the pantothenic acid and the biotin. Also introduced into the same hearings were data obtained by Williams and Higgins [301] which showed that young rats subsisting on human diets grew nearly as well when the flour quota of the diet—representing 25 per cent of the calories—was enriched flour as when this quota consisted of whole wheat flour.

The Committee on Food and Nutrition of the National Research Council also recommended iodization of table salt to a value of 1 part of potassium iodide or equivalent per 10,000 parts of salt and fortification of oleomargarine with vitamin A to a value of 9,000 international units to the pound (18,000 international units per kilogram). The committee encouraged the use of whole wheat bread and of butter but recommended that when these foods are not used, enriched flour and bread and properly fortified oleomargarine are preferred over unenriched white flour and bread and unfortified oleomargarine.

The Committee on Food and Nutrition made public on Oct. 1, 1941, the following recommendation as to policy in the matter of the addition of specific nutrients to foods:

Resolution Relating to Addition of Specific Nutrients to Foods Adopted by the Committee on Food and Nutrition at Its Meeting in Washington, October 1, 1941.[302]

WHEREAS there exist deficiencies of vitamins and minerals in the diets of significant segments of the population of the United States which cannot promptly be corrected by public education in the proper choice of foods, be it resolved, in order to correct and prevent such deficiencies:

(1) That the Committee endorses the addition of specific nutrients to staple foods (as indicated under 6 below) which are effective vehicles for correcting the above deficiencies in the diets of the general population or of significant age, geographical, economic or racial segments thereof;

299. Tobey, J. A., and Cathcart, W. H.: What's New in Home Economics, (Sept.) 1941.

300. Proceedings American Bakers' Association Conference, Boston, October 14, 1941.

301. Food and Drug Administration Hearings in the Matter of a Definition and Standard of Identity for Bread, July 7—August 15, 1941.

302. Minutes of the Committee on Food and Nutrition, National Research Council, Oct. 1, 1941. The Committee on Food and Nutrition has recently been reorganized and is now known as the Food and Nutrition Board of the National Research Council.

(2) That the Committee opposes the inclusion of additions of specific nutrients under definitions and standards which may be promulgated under the Food, Drug and Cosmetic Act except in the case of foods which constitute such effective vehicles of distribution;

(3) That the Committee favors unequivocally the fulfillment of the nutritional needs of the people by the use of natural foods as far as practicable and to that end encourages education in the proper choice of foods and the betterment of processes of food manufacture and preparation so as to retain more fully the essential nutrients native thereto;

(4) That to avoid undue artificiality of food supply the Committee favors whenever practicable the choice as vehicles for the corrective distribution of vitamins and minerals those foods which have suffered losses in refining processes and recommends that the vitamins and minerals added to such foods should preferably be the kinds and quantities native thereto in the unrefined state;

(5) That the addition of other than natural levels of vitamins and minerals to foods which are suitable as vehicles of distribution may be sanctioned when more natural routes are practically unavailable as measures to correct known nutritional deficiencies;

(6) That at present the Committee favors appropriate enrichment of flour and bread, (and perhaps corn meal), the fortification of milk with vitamin D, the suitable addition of vitamin A to table fats and of iodine to salt for dietary use. There is no information available to the Committee at the present time which indicates that it is desirable to recommend the addition of vitamins or minerals to foods other than those named;

(7) That specifically the Committee opposes the addition of synthetic vitamins to carbonated beverages and confectionery.

THE NATIONAL NUTRITION CONFERENCE FOR DEFENSE

This conference, called by the President of the United States, met in Washington, D. C., May 26 to 28, 1941.[303] It was attended by 700 invited delegates who represented the principal organizations, lay and public, with interests in nutrition. Scientists, educators, farmers, distributors, consumers and public officials in sectional and general meetings gave broad consideration to the questions raised by the problem of human needs for foods. They considered the question of the provision of satisfactory foods, first, as a measure of defense through improvement of the vigor and morale of the people of the United States; second, as a weapon of defense for all the democracies, and in particular Great Britain, and, third, as a basis for far reaching benefits to public health which in future years may accrue. As reported by Parran,[304] detailed agreement on methods, on lines of attack or on emphasis was not always obtained.

303. Proceedings of the National Nutrition Conference for Defense, Washington, D. C., Government Printing Office, to be published.

304. Parran, T.: Nutrition for National Defense, New Republic **104**:786-788 (June 9) 1941.

But the final recommendations, arrived at by the democratic processes of group give-and-take, represented basic practical next steps. Presented at the closing session of the conference by Dr. M. L. Wilson, director of the Division of Nutrition, Office of Defense Health and Welfare Services, they were unanimously adopted. In brief they called for the following actions:

1. The use of the standards prepared by the Committee on Food and Nutrition, both as the general goal for good nutrition in the United States and as the yardstick by which to measure progress.

2. Translation of these allowances, and other technical material, into terms of everyday foods and appetizing meals suitable for families and individuals at different economic levels.

3. Vigorous and continuous research to add to present knowledge of all aspects of nutrition.

4. More widespread education in nutrition of physicians, dentists, social service workers, teachers, etc.

5. The mobilization of every educational method to reach laymen by means of the schools, motion pictures, the radio, the public press, home and community demonstrations and all other suitable means.

6. Mobilization of all neighborhood, community, state and national organizations and services that can contribute in any way to raising the nutritional level of the people.

7. Vigorous and continued attack on the fundamental problems of unemployment, insecure employment and rates of pay inadequate to maintain an American standard of living.

8. Full use of any practical devices, such as the Food Stamp Plan, free school lunches and low cost milk distribution, which will bring nourishing, adequate meals to those who could not otherwise afford them and at the same time help to distribute food surpluses at a fair return to the farmer.

9. Efforts to improve food distribution, including processing, marketing, packaging and labeling, to bring about greater real economies for the consumer. These efforts would include vigorous prosecution of illegal practices.

10. Encouragement in all practical ways of greater production of the foods needed in more abundance—milk and milk products, eggs, vegetables, fruits and, in the case of many families, lean meats.

11. Encouragement in every practical way of more production for home use by rural people, especially those at low income levels.

12. The "enrichment" of certain staple food products, such as flour and bread, with nutritive elements that have been removed by modern milling and refining processes.

DISEASES OF METABOLISM

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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As in our review of last year, we shall summarize certain of the more significant contributions of the past year in the field of metabolic disturbances, with particular emphasis on the two most important disturbances of carbohydrate metabolism, diabetes mellitus and spontaneous hypoglycemia, as well as obesity, adrenal cortical insufficiency and disorders of the pituitary body and of the thyroid gland. Some discrimination had to be made in the selection of the articles referred to, since not all, as is usually true, were of equal merit. An effort has been made to give reference to both sides of controversial questions, without the formation of any conclusions on our part.

DIABETES MELLITUS

Carbohydrate Metabolism.—Fantl and his associates [1] recently have reported results of a detailed study of glycogen metabolism in the intact liver of the rabbit. Their work confirmed the essential points in Cori's [2] previous extensive observations on this same subject, namely, that the breakdown of glycogen to dextrose involves a series of well defined intermediate reactions in which phosphorylation of the intermediary products plays a major part.

Soskin [3] has continued his work on the importance of the hepatic regulation of the concentration of the sugar of the blood in connection with the disturbance of carbohydrate metabolism in diabetes mellitus. He reemphasized the fact that the diabetic animal can and does metabolize both carbohydrates and ketone bodies. In the absence of insulin, the

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1. Fantl, P.; Anderson, C. M., and Nelson, J. F.: Concerning Glycogen Breakdown in the Liver, Australian J. Exper. Biol. & M. Sc. **18**:369-377 (Dec.) 1940.

2. Cori, C. F.: Symposium on Carbohydrate Metabolism: Glycogen Breakdown and Synthesis in Animal Tissues, Endocrinology **26**:285-296 (Feb.) 1940.

3. Soskin, S.: The Blood Sugar: Its Origin, Regulation and Utilization. Physiol. Rev. **21**:140-193 (Jan.) 1941.

diabetic animal can utilize carbohydrates at any rate of which the normal animal is capable but utilizes less dextrose than the latter animal when the comparison is made at the same blood sugar level. Even this difference disappears above certain high blood sugar levels, whether or not insulin is present. Insulin merely modifies the relation between the concentration of the sugar in the blood and the rate of reaction, accelerating some phase of carbohydrate metabolism which proceeds slowly in its absence. Soskin pointed out that the threshold of stimulation of the hepatic mechanism, the so-called homeostatic mechanism on which regulation of the glycemic level depends, is in turn dependent on the balance between the blood sugar–lowering hormone, insulin, and the blood sugar–elevating hormones of the anterior lobe of the pituitary body and probably also those of the thyroid gland and of the adrenal cortex. Under certain circumstances, therefore, injected insulin may serve not to compensate for deficient secretion of the aforementioned hormone by the pancreas but to restore the endocrine balance to normal.

Endocrine Relation in Diabetes Mellitus.—Study of the relation of the anterior lobe of the pituitary body to the cause of diabetes mellitus has been continued by several investigators. Dohan and associates [4] have confirmed Richardson's [5] conclusion that the induction of permanent diabetes mellitus in experimental animals by the repeated injection of extract of the anterior lobe of the pituitary body is associated with atrophy of the islets of Langerhans, particularly of the beta cells. It is this atrophy which probably is responsible for the permanence of the diabetic state. Insulin therapy during the early months of this type of diabetes inhibited the rate of progress of the disease; fasting and fat feeding were followed by temporary diminution of the severity of the disease.

Gaebler and Galbraith [6] reported that in insulin-treated, depancreatized animals receiving constant diets a single large injection of a preparation of the anterior lobe of the pituitary body would produce hyperglycemia, increased glycosuria, ketonuria and hyperlipemia, along with loss of nitrogen. They stated that the dextrose-nitrogen ratios obtained for these animals permitted the assumption that the increase

4. Dohan, F. C.; Fish, C. A., and Lukens, F. D. W.: Induction and Course of Permanent Diabetes Produced by Anterior Pituitary Extract, Endocrinology **28**:341-357 (March) 1941.

5. Richardson, K. C.: Influence of Diabetogenic Anterior Pituitary Extracts of the Islets of Langerhans in Dogs, Proc. Roy. Soc., London, s.B **128**:153-169 (Jan. 4) 1940.

6. Gaebler, O. H., and Galbraith, H. W.: Effects of Anterior Pituitary Preparations in Experimental Pancreatic Diabetes, Endocrinology **28**:171-178 (Feb.) 1941.

in glycosuria was due to two factors, namely, increased formation of dextrose from protein and interference with the utilization of the dextrose thus produced.

Sakai [7] found glycosuria in 9 of 14 cases of acromegaly, in 3 of which hyperglycemia and the diabetic type of dextrose tolerance curve also were present. He expressed the belief that in the latter cases the disturbance in carbohydrate metabolism was extrainsular in origin and that it probably was related to the pituitary disturbance. Mayer and associates,[8] however, made perimetric studies on 65 unselected diabetic patients and found no evidence that hypertrophy of the pituitary body occurred in a significant number.

White [9] has reaffirmed her earlier statement that the anterior lobe of the pituitary body is hyperactive at the onset of diabetes in children and that subsequently it is hypoactive, so that in some instances a so-called pituitary type of dwarfism may ensue. She reported additional instances of this condition and expressed the belief that the injection of anterior pituitary extract greatly increased the rate of growth. Greene and co-workers [10] reported that extracts of the anterior lobe of the pituitary body increased the rate of growth and the sexual development of 3 young diabetic dwarfs; however, improved control of the diabetes was instituted along with the pituitary therapy and may have played a significant part in the improvement shown by these patients. Chase,[11] among others, argued that good control of the diabetes alone will enable diabetic children to grow and develop normally.

Several authors (Barnes and co-workers,[12] Spiegelman,[13] Cantilo [14]) have reported that the administration of estrogen either to depancreatized

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7. Sakai, T.: Studies on Function of Hypophysis in Carbohydrate Metabolism, Tokyo Igakkwai Zassi **55**:189-190 (March) 1941.

8. Mayer, L. L.; Strouse, C. D., and Soskin, S.: Lack of Perimetric Evidence for Pituitary Hypertrophy in Diabetes, J. Clin. Endocrinol. **1**:604-606 (July) 1941.

9. White, P.: Diabetes in Youth, New England J. Med. **224**:586-589 (April 3) 1941.

10. Greene, J. A.; January, L. E., and Swanson, L. W.: Effect of Extracts of Anterior Lobe of the Pituitary Gland on Diabetes, Retarded Growth and Sexual Development, J. A. M. A. **116**:2531 (May 31) 1941.

11. Chase, L. A.: Diabetes Mellitus: Problems of Its Control, Canad. M. A. J. **44**:250-255 (March) 1941.

12. Barnes, B. O.; Regan, J. F., and Nelson, W. O.: Improvement in Experimental Diabetes Following the Administration of Amniotin, J. A. M. A. **101**: 926-927 (Sept. 16) 1933.

13. Spiegelman, A. R.: Influence of Estrogen on the Insulin Requirement of the Diabetic, Proc. Soc. Exper. Biol. & Med. **43**:307-308 (Feb.) 1940.

14. Cantilo, E.: Successful Responses in Diabetes Mellitus of the Menopause Produced by Antagonistic Action of the Sex Hormones in Pituitary Activity, Endocrinology **28**:20-24 (Jan.) 1941.

animals or to diabetic patients reduces their requirement of insulin, presumably by suppression of the function of the anterior lobe of the pituitary gland. Lawrence and Madders,[15] however, reported negative results in their treatment of 5 diabetic women who were in the menopausal age group. These patients received 1 mg. of diethylstilbestrol four times daily for eight weeks. No change in their requirement of insulin was noted.

Not only hypophysectomy (Houssay and Biasotti[16]) but bilateral adrenalectomy (Long and associates[17]) has been reported to reduce the severity of diabetes in depancreatized animals. Furthermore, Hampton[18] found that patients who had Addison's disease were hypersensitive to injected insulin. It is therefore interesting to note Rhind and Wilson's[19] report of a fifteenth patient in whom Addison's disease and diabetes mellitus occurred simultaneously. These authors, however, expressed doubt that 5 of the 14 previously described patients could be considered authentically to have the two diseases. In the case which they reported, diabetes was discovered one year after the diagnosis of Addison's disease had been made and treatment with desoxycorticosterone acetate had been begun. As much as 60 units of regular insulin had been required daily for two months; then the patient died from an accidental overdose of insulin. At the postmortem examination atrophy of the adrenal bodies, fibrosis of the islets of Langerhans and a chromophobe adenoma of the pituitary body were found.

Diagnosis.—Results of recent examinations of a large number of young men for induction into the army again have called attention to the importance of careful study of those who exhibit glycosuria. Peel and Peel,[20] of Glasgow, Scotland, found that 43 of 115 recruits referred to them because of glycosuria had the diabetic type of dextrose tolerance curve. Beardwood[21] reported an even higher incidence of true diabetes mellitus among patients with glycosuria; he stated that only 8 to 10 per cent of these patients with glycosuria could be considered to have renal

15. Lawrence, R. D., and Madders, K.: Human Diabetes Treated with Oestrogens, Lancet **1**:601-602 (May 10) 1941.

16. Houssay, B. A., and Biasotti, A.: The Hypophysis, Carbohydrate Metabolism and Diabetes, Endocrinology **15**:511-523 (Nov.-Dec.) 1931.

17. Long, C. N. H.; Katzin, B., and Fry, E. G.: The Adrenal Cortex and Carbohydrate Metabolism, Endocrinology **26**:309-344 (Feb.) 1940.

18. Hampton, H. P.: Personal communication to the authors.

19. Rhind, E. G. G., and Wilson, A.: Diabetes Mellitus in Addison's Disease, Lancet **2**:37-38 (July 12) 1941.

20. Peel, A. A. F., and Peel, M. W.: Glycosuria in Recruits, Glasgow M. J. **17**:141-144 (May) 1941.

21. Beardwood, J. T., Jr.: Modern Diabetic Care, Pennsylvania M. J. **44**: 1022-1025 (May) 1941.

glycosuria. Joslin [22] stated that all patients with glycosuria should be reexamined at intervals, since in his experience true diabetes eventually will develop among 6 per cent of them. Yardumian and Alpern [23] reported that there was no fixed renal threshold for dextrose among persons as a group, either in health or in disease. The renal status, the concentration of sugar in the blood and the general condition of the patient (presence of infection, gangrene and the like) might cause rather wide fluctuations in his renal threshold for sugar.

Mortality Rate.—Records concerning diabetes collected from large clinics indicate that with the introduction of insulin diabetic coma has largely disappeared as a cause of death. Zisserman [24] found that diabetic coma was the cause of death in only 3.9 per cent of a series of patients whom he studied; coma accounted for only 3.3 per cent of the deaths in Dry and Tessmer's [25] series. On the other hand, insulin appears to have had no favorable effect on the mortality rate arising from cardiovascular complications. Data now available clearly indicate that cardiovascular disease is the chief cause of death of patients who have diabetes. Gangrene of the extremities ranked first and myocardial disease or involvement of the coronary arteries second in the statistics on mortality presented by several authors (Dillon,[26] Zisserman,[24] Pollack and associates,[27] Dry and Tessmer [25]). The principal reasons for these observations would seem to be (1) that the average diabetic patient's life span has been prolonged, so that he now reaches an age at which such vascular complications are common, and (2) that cardiovascular disturbances apparently develop among diabetic patients several years earlier than they do among nondiabetic persons (Beardwood,[21] Dry and Tessmer [25]).

Treatment.—Confirmation of the report by Tolstoi and Weber [28] in 1940 concerning the advisability of disregarding both hyperglycemia

22. Joslin, E. P.: Diabetic Hazards, New England J. Med. **224**:589-592 (April 3) 1941.

23. Yardumian, K. Y., and Alpern, A. N.: Clinical and Laboratory Observations on So-Called "Kidney Threshold for Glucose," Am. J. Clin. Path. **11**: 425-442 (May) 1941.

24. Zisserman, L.: Diabetes Mellitus: A Survey of One Hundred and Fifty-Five Deaths in Diabetic Patients, J. Clin. Endocrinol. **1**:314-315 (April) 1941.

25. Dry, T. J., and Tessmer, C. F.: Postmortem Findings in Cases of Diabetes, Minnesota Med. **24**:96-105 (Feb.) 1941.

26. Dillon, E. S.: Mortality Studies of Diabetes, Pennsylvania M. J. **44**: 1003-1007 (May) 1941.

27. Pollack, H.; Dolger, H., and Ellenberg, M.: An Analysis of the Diabetic Morbidity and Mortality in a General Hospital, Am. J. M. Sc. **202**:246-251 (Aug.) 1941.

28. Tolstoi, E., and Weber, F. C., Jr.: Protamine Zinc Insulin: A Clinical Study; Report of a Group of Diabetic Patients in Whose Cases Glycosuria Was Disregarded for One Year, Arch. Int. Med. **66**:670-678 (Sept.) 1940.

and glycosuria among patients treated with protamine zinc insulin has not appeared in recent literature. Many authors (Beardwood,[21] Marble,[29] Mitchell[30]) still insist on control not only of glycosuria but of hyperglycemia.

The possibility of a "cure" for early diabetes has been discussed this year by McDaniel and his associates.[31] They reported that early and vigorous treatment of diabetes by means of restricted carbohydrate diets and insulin "seemed" in some cases to have brought about an unexpected degree of amelioration of the severity of the disease. In other cases, however, such therapy brought about only the anticipated degree of improvement. The authors recommended the use of procedures designed to "rest" the pancreas, namely, fasting, feeding of fats and the taking of insulin to prevent degenerative changes in islet cells not already affected and to permit restoration of those exhausted cells which still retain the ability to recover.

In this respect the experiments of Richter and Schmidt[32] on depancreatized rats are of interest. These animals when allowed to select their own diet showed a marked appetite for fats and little appetite for carbohydrates. Either a great reduction in or a complete disappearance of both diabetic symptoms and hyperglycemia resulted from the ingestion of these self-selected diets. Normal rats already subsisting on self-selected diets at the time of pancreatectomy likewise exhibited an increased appetite for fats, and diabetic symptoms did not develop until the animals were fed standard rations.

Insulin.—Search continues for a type of insulin which can be administered effectively by mouth. Transient hypoglycemic effects have been observed among both animals and human beings to whom mixtures of unmodified insulin and agents designed to promote gastrointestinal absorption (quinine; hexylresorcinol) have been administered orally or rectally. Although huge doses (500 to 1,500 units) of insulin have been administered in this manner, the blood sugar–lowering effects have been so slight and so brief as to make the clinical use of such mixtures

29. Marble, A.: The Treatment of Diabetes with Diet and Insulin, New England J. Med. **224**:583-586 (April 3) 1941.

30. Mitchell, J. W.: Treatment of Diabetes in the Aged, Pennsylvania M. J. **44**:1015-1018 (May) 1941.

31. McDaniel, L. T.; Marble, A., and Joslin, E. P.: Can Diabetes Be "Cured" by Early, Vigorous Treatment? Connecticut M. J. **4**:710-718 (Dec.) 1940.

32. Richter, C. P., and Schmidt, E. C. H., Jr.: Increased Fat and Decreased Carbohydrate Appetite of Pancreatectomized Rats, Endocrinology **28**:179-192 (Feb.) 1941.

impracticable (Hanzlik and Cutting,[33] Cutting and Robson,[34] Driver and Murlin [35]).

Additional studies on the subcutaneous implantation of pellets of insulin in combination with cholesterol or lecithin have been carried out by Cutting and associates.[36] In some instances the hypoglycemic effects of such pellets implanted in dogs lasted as long as thirteen days, but irregularities of absorption were too great to justify clinical trial of the pellets.

There is still argument as to the ideal type of insulin or mixtures of insulin for subcutaneous injection. In general, mixtures of unmodified insulin and protamine zinc insulin have come into more widespread use. Results of extensive studies on such mixtures recently have been reported by Ulrich.[37] He studied blood sugar curves of a group of diabetic patients to whom were given on different days protamine zinc insulin alone, protamine zinc insulin and unmodified insulin in separate sites and protamine zinc insulin and unmodified insulin in mixtures containing various proportions of each type. Curves were obtained for these patients when they were in the fasting state and when they were fed the usual three meals during the day. In each instance the same total dose of insulin, 40 units, was given. The blood sugar curves obtained in this series of experiments showed that mixtures of the two types of insulin produced a less immediate hypoglycemic effect than did regular insulin injected separately but a greater immediate effect than did protamine zinc insulin given alone. The mixtures produced a more uniform and a more readily predictable action throughout the day than did the two types of insulin given in separate sites; a mixture of 3 parts of unmodified insulin with 2 parts of protamine zinc insulin gave the best results. In such mixtures, the author suggested, regular insulin was loosely combined with protamine zinc insulin.

Recently Johlin [38] reported that the subcutaneous injection into experimental animals of a suspension in physiologic solution of sodium chloride of the precipitate formed when crystalline zinc insulin is shaken

33. Hanzlik, P. J., and Cutting, W. C.: Agents Promoting Gastrointestinal Absorption of Insulin, Endocrinology **28**:368-374 (March) 1941.

34. Cutting, W. C., and Robson, G. B.: Clinical Trials with Insulin-Quinine Mixtures by Mouth in Diabetics, Endocrinology **28**:375-377 (March) 1941.

35. Driver, R. L., and Murlin, J. R.: Factors in Absorption of Insulin from the Alimentary Tract, Am. J. Physiol. **132**:281-292 (Feb.) 1941.

36. Cutting, W. C.; Morton, M. C., and Cohn, R. B.: Subcutaneous Administration of Insulin by Pellets, Endocrinology **28**:679-680 (April) 1941.

37. Ulrich, H.: Clinical Experiments with Mixtures of Standard and Protamine Zinc Insulins, Ann. Int. Med. **14**:1166-1179 (Jan.) 1941.

38. Johlin, J. M.: The Attenuation of Insulin by Adsorption, Endocrinology **29**:574-576 (Oct.) 1941.

for several hours with pure chloroform resulted in a reduced but prolonged hypoglycemic action, similar to that produced by other insoluble insulin preparations, such as protamine zinc insulin. This preparation has not been used clinically.

The question of the patient's resistance to insulin has been reviewed by several authors (Martin and associates,[39] Hart and Vicens [40]). In most of the cases reported, resistance to large doses of insulin was found in association with urticarial lesions. They recommended that massive doses of insulin be administered until the period of resistance has been overcome.

Diabetic Coma.—Mirsky and his collaborators [41] asserted that an excessive intake of carbohydrates will not accelerate the production of acetone bodies and thereby induce diabetic coma. They stated that acetone bodies are formed as the result of depletion of the glycogen reserves of the liver; in depancreatized dogs the administration of large amounts of dextrose, even in the absence of injected insulin, will cause the production of acetone bodies to cease. Likewise, in a group of patients who had severe diabetes mellitus and who received only enough insulin to prevent the development of a precoma state, the feeding of large amounts of carbohydrates (as much as 1,000 Gm. daily) markedly reduced the ketonuria which was present. According to the opinion expressed by these investigators, deprivation of insulin was the most important factor in the development of acidosis.

On the other hand, Cole [42] found that in 13 episodes of coma which occurred among 24 young diabetic patients acute infectious processes had been responsible in 9 instances and failure to take insulin in only 4 instances.

Duncan [43] has contributed an excellent review of the therapeutic measures to be employed in diabetic coma. He expressed a preference for the administration of both protamine zinc insulin and regular insulin at the start of treatment, to be followed every hour thereafter by the administration of 20 to 30 units of the regular type until the carbon

39. Martin, W. P.; Martin, H. E.; Lyster, R. W., and Strouse, S.: Insulin Resistance: Critical Survey of the Literature with the Report of a Case, J. Clin. Endocrinol. **1**:387-398 (May) 1941.

40. Hart, J. F., and Vicens, C. A.: Association of Extreme Insulin Resistance with Allergy: Report of a Case, J. Clin. Endocrinol. **1**:399-401 (May) 1941.

41. Mirsky, I. A.; Franzblau, A. N.; Nelson, N., and Nelson, W. E.: Diabetes Mellitus: The Role of Excessive Carbohydrate Intake in the Etiology of Diabetic Coma, J. Clin. Endocrinol. **1**:307-313 (April) 1941.

42. Cole, L.: Diabetic Coma in a Series of Young Diabetics, Brit. M. J. **1**:882-884 (June 14) 1941.

43. Duncan, G. G.: Diabetic Coma (Ketosis), Pennsylvania M. J. **44**:725-727 (March) 1941.

dioxide–combining power of the blood increases to more than 30 volumes per cent. He administered sodium lactate intravenously to patients whose carbon dioxide–combining power either was low at the onset or did not increase after a suitable period of treatment. Krarup [44] reported that anuria and uremia in the presence of diabetic coma result from a deficiency in the fixed base; consequently, he recommended the intravenous administration of solutions of sodium bicarbonate as a means of restoration of renal function to normal.

Diabetes and Surgical Operations.—Close cooperation between internist and surgeon has made almost any type of surgical procedure as safe for the diabetic patient as it is for the nondiabetic patient. Recent extensive reviews of the subject of operation on the diabetic patient have been presented by Tyler [45] and Bothe.[46] Both of these authors emphasized the importance of careful preoperative preparation of the diabetic patient. When operation is urgent, the only preparation possible may be vigorous therapy directed toward reduction of acidosis, if it is present. The adequate intravenous administration of fluids, including solutions of dextrose, and insulin therapy were recommended. Delay of the operation, when this was possible, until such time as both hyperglycemia and glycosuria had been controlled and the hepatic stores of glycogen had been replenished, with the feeding of added carbohydrates, yielded optimal results. Both authors, however, agreed that early intervention in cases complicated by an infectious process was desirable, not only for relief of the local condition but for more rapid control of the diabetes. They stated that either spinal or local anesthesia was preferable to general anesthesia, the latter of which would tend further to deplete hepatic stores of glycogen and thus increase the likelihood of acidosis. Bothe reported that in a group of 14,000 diabetic patients of all ages who underwent many types of surgical procedures the mortality rate amounted to only 5 per cent.

Erb [47] advised the more frequent employment of conservative procedures rather than radical amputation in the presence of gangrene of the extremities among diabetic patients. Bothe expressed the opinion that for 40 per cent of such patients limited measures, such as incision and drainage or amputation of one digit, would suffice. In Erb's series

44. Krarup, N. B.: Alkali Treatment in Diabetic Coma with Hyperazotemia and Anuria, Ugesk. f. læger **102**:27, 1940; abstracted, J. Clin. Endocrinol. **1**:630 (July) 1941.

45. Tyler, G. T., Jr.: Surgery in Diabetes, South. Med. & Surg. **103**:6-8 (Jan.) 1941.

46. Bothe, F. A.: The Surgical Diabetic, Pennsylvania M. J. **44**:1018-1021 (May) 1941.

47. Erb, W. H.: Conservative Surgery in Diabetic Gangrene, Pennsylvania M. J. **44**:1131-1134 (June) 1941.

local procedures saved the limb in 50 per cent of patients. However, both writers agreed that conservative therapy is to be attempted only for those patients whose vessels (in the extremities) are competent. In the presence of severe degrees of arteriosclerosis, radical amputation to as far as the zone of adequate circulation was called the procedure of choice. In a recent review in *The Journal of the American Medical Association* [48] the indications for each type of amputation for diabetic gangrene were described. In general, the indications given for radical amputation were septicemia secondary to the gangrene, rapidly extending infections and extensive sepsis in a debilitated patient.

Diabetes and Pregnancy.—Little has been added to this subject since the writing of last year's review. White [49] and Smith and Smith [50] have reviewed their experience with the toxemias of pregnancy both among diabetic and among nondiabetic patients and have concluded that the elevated value for chorionic gonadotropin in the serum of such patients is due to disturbed metabolism of estrogen involving greater and more rapid destruction of this hormone. White's suggestion that hormonal imbalance is responsible for the toxemias of pregnancy and that replacement therapy with progestin and estrogen is indicated has been criticized by Hurwitz.[51] He stated that her work had been inadequately controlled and that accidents of pregnancy also occurred among diabetic women who had a normal hormonal balance. He added that he had been able to obtain as good results in his series without substitution therapy as did White in her series of treated patients. White [49] and Joslin [52] replied that they had not felt justified in increasing their series of untreated patients, since the fetal survival rate in this group was less than half that in the treated group.

Hurwitz also denied that routine cesarian section was advisable for pregnant diabetic women. He reported a fetal mortality rate of 15 per cent among 53 diabetic women who were allowed to give birth to their infants spontaneously, a rate which compared favorably with that given by White and her associates for their treated patients. Porter [53] and Nothmann,[54] however, reported that fetal hypoglycemia, caused by

48. Amputation in Diabetes Mellitus and Peripheral Vascular Disease, Council on Physical Therapy, J. A. M. A. **117**:1095-1097 (Sept. 27) 1941.

49. White, P.: Reply to Hurwitz, J. A. M. A. **116**:645 (Feb. 15) 1941.

50. Smith, G. V., and Smith, O. W.: Estrogen and Progestin Metabolism in Pregnancy: II. The Endocrine Inbalance of Preeclampsia and Eclampsia; Summary of Findings to February, 1941, J. Clin. Endocrinol. **1**:470-476 (June) 1941.

51. Hurwitz, D.: Pregnancy Accidents in Diabetes, J. A. M. A. **116**:645 (Feb. 15) 1941.

52. Joslin, E. P.: Reply to Hurwitz, J. A. M. A. **116**:645-646 (Feb. 15) 1941.

53. Porter, R. D.: Management of Pregnancy in Diabetes, Pennsylvania M. J. **44**:1011-1013 (May) 1941.

54. Nothmann, M.: Diabetes Mellitus and Pregnancy, New England J. Med. **224**:275-280 (Feb. 13) 1941.

hypertrophy of the islets of Langerhans in the infant, occurred so frequently that section during the latter part of the ninth month of pregnancy is indicated. Potter and co-workers [55] reviewed the observations made at necropsy on the pancreases of 26 infants whose mothers had diabetes, of 3 infants whose mothers seemed questionably to have diabetes and of 16 infants whose mothers did not have diabetes. They concluded that an increase in fetal islet tissue may be found either in the presence or in the absence of abnormal sugar metabolism in the mother and that there is no correlation either between the severity or the degree of control of diabetes in the mother and the increase in the islet tissue or between the amount of islet tissue found at necropsy and the infant's blood sugar level prior to death.

Miscellaneous Complications.—Lamb and Keltz [56] reviewed the dermatologic complications of diabetes mellitus; they concluded that control of the diabetes is the most important therapeutic measure under such circumstances.

McKee [57] found that among 2,360 diabetic patients on whom funduscopic examination was done there were 476 (21.7 per cent) who exhibited retinal changes which could be "more or less" related to their diabetes; 8.6 per cent of these 476 patients exhibited typical diabetic retinitis, and 43 per cent exhibited retinal arteriosclerosis. There was only 1 instance of lipaemia retinalis in the entire group.

A syndrome which has been recognized recently in association with diabetes mellitus is that of so-called intercapillary glomerulosclerosis. This was first described in 1936 by Kimmelstiel and Wilson,[58] who reported that among patients who had presented a picture of diabetes mellitus (usually of long duration), edema of the nephrotic type, gross albuminuria and varying degrees of hypertension, postmortem examination of the kidneys disclosed a characteristic deposition of hyaline material between the capillaries of the glomerular tufts. Porter and Walker [59] recently reviewed this subject and reported that in addition to those clinical features mentioned by Kimmelstiel and Wilson, 100 per cent of their patients had retinal changes associated with arteriosclerosis,

55. Potter, E. L.; Seckel, H. P. G., and Stryker, W. A.: Hypertrophy and Hyperplasia of Islets of Langerhans of the Fetus and of the Newborn Infant, Arch. Path. **31**:467-482 (April) 1941.

56. Lamb, J. H., and Keltz, B. F.: Skin Manifestations in Diabetes Mellitus, J. Oklahoma M. A. **34**:93-97 (March) 1941.

57. McKee, S. H.: Examination of Fundus in 2,360 Diabetics, Canad. M. A. J. **45**:127-129 (Aug.) 1941.

58. Kimmelstiel, P., and Wilson, C.: Intercapillary Lesions in the Glomeruli of the Kidney, Am. J. Path. **12**:83-98 (Jan.) 1936.

59. Porter, W. B., and Walker, H.: The Clinical Syndrome Associated with Intercapillary Glomerulosclerosis, J. A. M. A. **116**:459-463 (Feb. 8) 1941.

whereas 50 per cent of them had the punctate hemorrhages and exudates characteristic of diabetic retinitis. They outlined the sequence of events under such circumstances as follows: (1) mild diabetes occurring in a patient past 40 years of age; (2) the appearance, usually within the next three years, of albuminuria, mild edema and hypoproteinemia and arteriosclerosis; (3) exaggeration of the symptoms and the development of hypertension within the next five years, and (4) death a few months later of the renal and vascular complications. The authors suggested that arterial and arteriolar degeneration perhaps was the underlying factor in the entire syndrome, including the diabetes.

Siegel and Allen [60] found these renal lesions among 33.3 per cent of 105 diabetic patients on whom necropsy was performed. The retinitis of diabetes was found among all the patients who had presented nephrotic symptoms. The authors expressed the belief that the diabetic lesion could be easily distinguished microscopically from glomerulosclerotic and nephrosclerotic lesions among nondiabetic patients and that the lesion was a focal intramural type of glomerulosclerosis arising within the capillary walls rather than between these walls, as has been previously reported.

Several authorities [61] have recorded the frequency of disease of the gallbladder among diabetic patients. Rhodes [62] and Thomason,[63] however, reported that acute pancreatitis or pancreatic lithiasis rarely terminates in diabetes mellitus.

SPONTANEOUS HYPOGLYCEMIA

Additional reports of spontaneous hypoglycemia continue to appear in the literature. Waddell and Humphries [64] concluded that this condition was not uncommon, since they encountered 6 instances of it among children within two and a half years. Sandler [65] stated: "Chronic hypoglycemia is a common disorder masquerading as pseudoulcer, chronic appendicitis, abdominal migraine, neuro-circulatory asthenia, etc." He reported on 6 patients who had undergone one or more major abdominal

60. Siegel, S., and Allen, A. C.: Intercapillary Glomerulosclerosis (Kimmelstiel-Wilson) and Nephrotic Syndrome in Diabetes Mellitus, Am. J. M. Sc. **201**:516-528 (April) 1941.

61. Zisserman.[24] Dry and Tessmer.[25] Tyler.[45]

62. Rhodes, G. K.: Acute Pancreatitis: Thirty-Five Cases with Observations on Blood Amylase Studies, West. J. Surg. **49**:266-270 (May) 1941.

63. Thomason, T. H.: Pancreatic Lithiasis with Diabetics: Report of Four Cases, South. Surgeon **10**:135-143 (Feb.) 1941.

64. Waddell, W. W., Jr., and Humphries, T. J.: Spontaneous Hypoglycemia in Childhood, Virginia M. Monthly **68**:440-448 (Aug.) 1941.

65. Sandler, B. P.: Chronic Abdominal Pain Due to Hypoglycemia with Note on Pathogenesis of Neurotic Symptomatology, Surgery **9**:331-348 (March) 1941.

operations, without relief, for recurrent episodes of abdominal pain. Additional inquiry into their histories revealed in each instance that pain was associated with symptoms of hypoglycemia (sweating, faintness, dizziness and the like); all were relieved of their symptoms when they subsisted on a low carbohydrate, high protein diet. None of these patients underwent surgical exploration for pancreatic tumor.

Allen [66] has stated that in most cases hyperinsulinism is mild and that it represents a disorderly rather than an excessive secretion of insulin; he expressed the belief, therefore, that the condition should be termed "dysinsulinism" rather than "hyperinsulinism." He doubted that small islet cell tumors could flood the body with as much insulin as would be required to produce the symptoms encountered among these patients, because epinephrine will prevent attacks. He doubted that this drug could serve as an antidote to a large excess of insulin by releasing dextrose from the liver. Furthermore, high protein diets have been reported to prevent attacks, and no person could eat enough protein to protect against a large excess of insulin. Either a single large dose or repeated small excessive doses of insulin ultimately result in toxicity, with nausea, vomiting and prostration, not relieved by the administration of dextrose, but these symptoms were not seen among patients who had spontaneous hypoglycemia. For these reasons, he did not advise routine surgical exploration of the pancreas in these patients; instead, he recommended high carbohydrate diets, which could be made to contain relatively few calories if the patient became greatly overweight.

On the other hand, several recently reported instances of spontaneous hypoglycemia associated with proved (at surgical exploration or necropsy) islet cell tumors have brought the number of recorded cases of this syndrome to considerably more than 100.[67] In most instances removal of the pancreatic tumor was followed by cessation of the attacks of hypoglycemia. Indeed, Rowntree [68] and Windfeld [69] recommended surgical exploration of the pancreas for all patients who presented proved

66. Allen, F. M.: Hyperinsulinism: Spontaneous and Artificial Hyperinsulinism, J. Clin. Endocrinol. **1**:595-603 (July) 1941.

67. Frantz, V. K.: Tumors of Islets of Langerhans with Hyperinsulinism, New York State J. Med. **41**:881-882 (April 15) 1941. Brunschwig, A.: Large Islet-Cell Tumor of Pancreas, Surgery **9**:554-560 (April) 1941. Flinn, L. B.; Beatty, G. A.; Ginsberg, M., and Hemsath, F. A.: Carcinoma of the Islands of Langerhans, with Hypoglycemia and Metastasis of the Liver, J. A. M. A. **117**: 283-285 (July 26) 1941. Meyer, K. A.; Amtman, L., and Perlman, L.: Islet Cell Tumor of the Pancreas: Report of Case, ibid. **117**:16-20 (July 5) 1941.

68. Rowntree, L. G.: Hyperinsulinism, J. M. Soc. New Jersey **38**:301-305 (June) 1941.

69. Windfeld, P.: Surgical Treatment of Pancreas Adenomas Producing Insulin (Insulinomas), Ugesk. f. læger **103**:353 (March 20) 1941; abstracted, J. A. M. A. **117**:972 (Sept. 13) 1941.

hypoglycemia. Rowntree reported that subtotal pancreatectomy was beneficial for patients in whom no tumor was found. Windfeld, however, expressed the opposite view. Burtness and associates [70] reported that a probable diagnosis of pancreatic tumor is indicated for those patients among whom results of the test for tolerance to insulin show only slight sensitivity to insulin, that is, when the value for blood sugar decreases little throughout the test and then slowly returns to normal.

Malignant changes in islet cell tumors have been reported relatively often; such changes occurred in 21 of 96 cases found in the literature by Frantz. Flinn and his associates, however, found only 4 instances of metastasizing pancreatic islet tumors in the literature and reported a fifth case.

OBESITY

Bauer [71] reviewed the subject of obesity and concluded:

> Obesity is a compulsory tendency toward marked overweight due to abnormal accumulation of fat by persons who are left alone to their automatic regulation and are not supervised as far as the intake of food and expenditure of energy are concerned.

Such a condition he related to an abnormal gene complex, rather than to simple caloric excesses in the diet. He agreed, however, that a submaintenance diet was the only practical form of therapy for these patients.

Bruch [72] warned against the treatment of obesity with glandular preparations, particularly among children. Short [73] reported a case in which a 35 year old woman lost 300 pounds (about 136 Kg.) in eighteen months when she was maintained on a 600 to 800 calory diet. Her basal metabolic rate, which had been elevated, and her dextrose tolerance curve, which had been of the diabetic type, both returned to normal after the reduction in weight.

Handelsman and Gordon [74] reported that patients in whom obesity and true hypothyroidism coexist are rare; the majority of obese patients, he stated, could receive large doses of thyroid for short intervals with

70. Burtness, H. I.; Koehler, A. E., and Saint, J. H.: Hyperinsulinism Due to Adenoma of Islets of Langerhans: Case Report with Metabolic Studies Before and After Removal of Tumor, Ann. Int. Med. **14**:1915-1932 (April) 1941.

71. Bauer, J.: Obesity: Its Pathogenesis, Etiology, and Treatment, Arch. Int. Med. **67**:968-994 (May) 1941.

72. Bruch, H.: Obesity in Childhood and Endocrine Treatment, J. Pediat. **18**:36-56 (Jan.) 1941.

73. Short, J. J.: Rapid Weight Reductions: Loss of Three Hundred Pounds in Eighteen Months; Report of a Case, J. A. M. A. **117**:506-510 (Aug. 16) 1941.

74. Handelsman, M. B., and Gordon, M. B.: Obesity: The Calorigenic Action of Thyroid Substance in Obese Patients, J. Clin. Endocrinol. **1**:612-619 (July) 1941.

relatively slight or no calorigenic effect. Andersen,[75] however, reported on 3 patients in all of whom severe thyrotoxicosis and auricular fibrillation developed after the administration of large amounts of thyroid for obesity. Bram [76] reported 54 instances in which exophthalmic goiter had followed drastic reduction of weight and stated that this sequel was particularly likely to develop among those patients who took thyroid along with the diet.

THYROID GLAND

McClendon and Foster [77] determined the content of thyroxin iodine in the blood of 373 patients and reported that for every microgram of thyroxin iodine in 100 cc. of whole blood there was about 1 mg. of thyroxin in the body of an adult person weighing 65 Kg. Their figures showed that a direct relation existed between the micrograms of thyroxin iodine in 100 cc. of whole blood and the patient's basal metabolic rate. Consequently, they expressed the belief that such determinations could be used as a check on the reliability of any individual basal metabolic rate, or even as a substitute for the basal metabolic rate. They cautioned, however, that the previous use of either yellow mercurous iodide or radiopaque oil (iodized poppyseed oil) would lead to errors in determination of iodine in the blood.

Dunlap [78] presented an extensive review of the states associated with low basal metabolic rate. He classified them as "primary hypothyroidism" myxedema or creatinism, and "secondary hypothyroidism," hypometabolism without myxedema. The latter classification included the majority of patients found to have low basal metabolic rates. Although the cause of primary hypothyroidism is, of course, deficient secretion by the thyroid gland, the underlying factor in the secondary type of hypothyroidism has been less well understood. Pituitary deficiency conceivably might play a role. Some types of secondary hypothyroidism respond well to replacement therapy with thyroid. Among these the author included such conditions as menstrual disturbances not related to pelvic disease,[79] sterility, habitual abortion, anorexia nervosa

75. Andersen, W. T.: Three Cases of Hyperthyroidism After Weight-Reducing Thyroidin Treatment, Acta med. Scandinav. **104**:589-598, 1940.

76. Bram, I.: Weight Reduction as an Exciting Cause of Exophthalmic Goiter, M. Rec. **152**:437-439 (Dec. 18) 1940.

77. McClendon, J. F., and Foster, W. C.: Thyroid Hormone in the Blood and Tissues in Relation to Basal Metabolic Rate, Endocrinology **28**:412-418 (March) 1941.

78. Dunlap, H. F.: The Clinical Significance and Treatment of States Associated with Low Basal Metabolic Rates, J. Indiana M. A. **34**:73-77 (Feb.) 1941.

79. Haines, S. F., and Mussey, R. D.: Certain Menstrual Disturbances Associated with Low Basal Metabolic Rates Without Myxedema, J. A. M. A. **105**: 557-560 (Aug. 24) 1935.

and certain other nutritional disturbances. Usually, increase in the basal metabolism required the administration of large doses of thyroid.

Hertz and Galli-Mainini [80] reported that overgrowth was a constant observation among 121 juvenile patients who had thyrotoxicosis and that the overgrowth appeared to coincide with the normal peaks of growth. They suggested that excessive secretion by the thyroid gland might have acted as a synergist to the growth factor of the anterior lobe of the pituitary and that, therefore, thyroid might be useful in the treatment of persons whose height is less than normal. On the other hand, Beard [81] reported that the simultaneous administration of desiccated thyroid and anterior pituitary extract containing the growth factor to a cretin 16 years old produced no more growth than could be obtained by administration of the thyroid alone.

Cutler and Hoerr [82] have reported results of a five year follow-up study of 57 patients with cardiac disease who underwent total thyroidectomy. They concluded that for a selected group of patients suffering from angina pectoris, excluding those with evidence of congestive heart failure or cardiac enlargement, the operation offered considerable hope of relief of symptoms. Berlin and associates,[83] in a similar review of seven and a half years' experience with total thyroidectomy for chronic cardiac disease, concluded that this procedure was beneficial to "a certain group of patients for whom life was quite intolerable before operation because of complete invalidism due to congestive failure or severe repeated attacks of excruciating chest pain at bed rest or on slight exertion."

ADRENAL CORTEX

Several comprehensive reviews of the progress which has been made in the treatment of adrenal cortical insufficiency recently have appeared.[84]

80. Hertz, S., and Galli-Mainini, C.: Effect of Thyroid Hormone on Growth in Thyrotoxic and Myxedematous Children and Adolescents, J. Clin. Endocrinol. **1**:518-522 (June) 1941.

81. Beard, E. E.: Cretinism: Lack of Response to Anterior Pituitary Growth Principle, J. Clin. Endocrinol. **1**:293-296 (April) 1941.

82. Cutler, E. C., and Hoerr, S. O.: Total Thyroidectomy for Heart Disease: A Five Year Follow-Up Study, Ann. Surg. **113**:245-259 (Feb.) 1941.

83. Berlin, D. D.; Riseman, J. E. F., and Blumgart, H. L.: The Present Status of Total Thyroidectomy: A Review of Seven and One-Half Years' Experience, Tr. Am. A. Study Goiter, 1940, pp. 1-6.

84. (*a*) Loeb, R. F.: Adrenal Cortex Insufficiency, J. A. M. A. **116**:2495-2500 (May 31) 1941. (*b*) Thorn, G. W.: Treatment of Addison's Disease, J. Clin. Endocrinol. **1**:76-81 (Jan.) 1941. (*c*) Hampton, H. P., and Kepler, E. J.: Addison's Disease: Treatment and Prognosis, Am. J. M. Sc. **202**:264-271 (Aug.) 1941. (*d*) McGavack, T. H.: Adrenal Insufficiency: Some Pitfalls in the Treatment of Addison's Disease, J. Clin. Endocrinol. **1**:68-75 (Jan.) 1941. (*e*) Kepler, E. J., and Willson, D. M.: Diseases of the Adrenal Glands: I. Addison's Disease, Arch. Int. Med. **68**:979-1009 (Nov.) 1941.

Desoxycorticosterone acetate in oil injected intramuscularly has largely supplanted other replacement therapy in the treatment of Addison's disease. Most authors have recommended that the drug be given in amounts ranging from 2 to 5 mg. per day. In association with the synthetic compounds, administration of 2 to 5 Gm. of extra sodium chloride plus the ingestion of a liberal diet, which may be a general, high vitamin, high calory diet, a high protein diet or a high carbohydrate diet, has been employed. The pitfalls of treatment with desoxycorticosterone acetate, however, have been reemphasized by McGavack.[84d] He warned that the appearance of edema of the extremities, rapid gain in weight, increase in blood pressure and, finally, cardiac and circulatory embarrassment, are indications that the dosage of the drug or of the extra salt or perhaps of both is excessive. Willson, Dry and one of us (E. H. R.)[85] recently reported an instance of cardiac failure after the treatment of Addison's disease with desoxycorticosterone acetate, a report which well illustrates the potential dangers involved in the use of this drug. Most authorities have reported that administration of the aqueous extract of the whole cortex is still the most effective treatment of crises of adrenal insufficiency. Furthermore, it should be emphasized that for a certain small group of patients who have Addison's disease the synthetic preparation has proved to be ineffective; these patients often do well when they are treated with the whole cortical extract.

Britton and Kline [86] reported that desoxycorticosterone acetate acted too slowly in adrenalectomized cats to be effective in the immediate treatment of severe degrees of adrenal insufficiency. In addition, both these authors and others [87] have found the synthetic preparation to be much less effective in restoration of values for blood sugar and for glycogen in the liver to normal than is whole cortical extract.

In 1940 Anderson and his associates [88] reported the successful treatment of 6 patients suffering from Addison's disease by means of the sublingual administration of 2 to 6 mg. of desoxycorticosterone acetate dissolved in propylene glycol and given in divided doses. Turnoff and Rowntree [89] recently reported that 2 patients who had advanced adrenal

85. Willson, D. M.; Rynearson, E. H., and Dry, T. J.: Cardiac Failure Following Treatment of Addison's Disease with Desoxycorticosterone Acetate, Proc. Staff Meet., Mayo Clin. **16**:168-173 (March 12) 1941.

86. Britton, S. W., and Kline, R. F.: Relative Effects of Desoxycorticosterone and Whole Corticoadrenal Extract on Adrenal Insufficiency, Am. J. Physiol. **133**: 503-510 (July) 1941.

87. Cleghorn, R. A.; Fowler, J. L. A.; Wenzel, J. S., and Clarke, A. P. W.: The Desoxycorticosterone Acetate Requirement of the Adrenalectomized Dog, Endocrinology **29**:535-544 (Oct.) 1941. McGavack.[84d]

88. Anderson, E.; Haymaker, W., and Henderson, E.: Successful Sublingual Therapy in Addison's Disease, J. A. M. A. **115**:2167-2168 (Dec. 21) 1940.

89. Turnoff, D., and Rowntree, L. G.: Successful Sublingual Therapy in Addison's Disease: A Confirmative Report, J. A. M. A. **116**:2016 (May 3) 1941.

insufficiency were satisfactorily maintained on 1 mg. of the drug dissolved in propylene glycol, taken six to seven times daily. The patients were directed to hold the drug under the tongue for fifteen minutes and then to expectorate it. Sodium chloride was not added to their diet. Not all investigators, however, have found the oral route to be as effective as the intramuscular route in the administration of the drug. Thompson [90] reported that when desoxycorticosterone acetate was given orally it was only about 20 per cent as effective as it is when it is given by injection. Despite these contrary reports, it is probable that the convenience of a preparation to be used orally will lead to extensive employment of it, particularly when improved methods of synthesis of the drug make it available in larger amounts.

The subcutaneous implantation of pellets containing the synthetic substance was reported [91] to have been successful at about the same time that reports of the effective oral administration of the drug appeared in the literature. Patients who have been successfully treated in this manner have been stabilized first by the daily injection of the synthetic compound in oil. Wilder [92] has stated that the period of stabilization should extend over at least six months. When the daily maintenance dose has been determined, the amount of the drug calculated to be sufficient to maintain the patient for several months is implanted in several pellets beneath the skin. Thorn and associates [93] have given a method for the determination of the number and content of the pellets which will permit absorption at the desired rate. Edema among the patients has been controlled by reduction of their intake of salt.

In final consideration of the treatment of Addison's disease with desoxycorticosterone acetate by whatever route of administration, it should be emphasized that this drug represents only one of the fractions contained in the whole cortical extract. Its administration does not, therefore, constitute complete replacement therapy, and therein lies the explanation of its failure to benefit all patients who have adrenal insufficiency. Not until either a much more potent whole cortical extract

90. Thompson, W. O., discussion on Thorn.[84b]

91. Billmann, F., and Grathwohl, F. D.: Efficacy of Subcutaneous Implantation of Tablets of Crystalline Desoxycorticosterone Acetate on Bilaterally Adrenalectomized Dogs, Klin. Wchnschr. **19**:1030-1033 (Oct. 5) 1940. Moehlig, R. C.: Addison's Disease Treated by Implantation of Desoxycorticosterone Acetate Pellets, Endocrinology **27**:633-637 (Oct.) 1940. Segall, G.: Treatment of Addisons' Disease with Pellets of Synthetic Desoxycorticosterone Acetate Implanted Subcutaneously, Am. J. M. Sc. **201**:202-208 (Feb.) 1941.

92. Wilder, R. M., in discussion on Thorn.[84b]

93. Thorn, G. W.; Howard, R. P.; Emerson, K., Jr., and Firor, W. M.: Treatment of Addison's Disease with Pellets of Crystalline Adrenal Cortical Hormone (Synthetic Desoxycorticosterone Acetate) Implanted Subcutaneously, Bull. Johns Hopkins Hosp. **64**:339-365 (May) 1939.

or adequate amounts of each of the individual compounds elaborated by the adrenal cortex are available will entirely satisfactory results be obtained for these patients.

The treatment of patients who have Addison's disease by means of grafts of the adrenal gland has been reported in 5 cases, according to Katz and Mainzer.[94] They added a sixth instance to the literature. An adrenal gland from a patient who had just died of a cerebral neoplasm was grafted into the abdominal muscles of a patient who had advanced adrenal insufficiency. After the latter patient had recovered from the immediate effects of the operation, his blood pressure was maintained and his general condition was excellent for a period of fifteen months of observation.

The role of the adrenal glands in relation to shock has been subjected to considerable scrutiny. Swingle and associates[95] reported that desoxycorticosterone acetate would protect adrenalectomized dogs against traumatic shock. They suggested that the normal adrenal cortex was necessary in some way for the maintenance of the normal ability of the periphery to cope with vascular strain. Rhoads and co-workers[96] reported that the intravenous administration of cortical extract to patients who had extensive burns reduced the amount of blood plasma which was required to restore the circulation to normal, presumably by reducing the amount of plasma protein which escaped through the capillaries into the interstitial fluid. They suggested that capillary permeability might have been altered by the cortical extract. Besser,[97] however, reported that the preoperative administration of 5 to 10 mg. of desoxycorticosterone acetate, in three separate doses twelve, six and four hours prior to surgical operation, did not reduce the incidence of surgical shock. He said that 31 per cent of 72 patients so treated exhibited shock, as evidenced by systolic blood pressures of less than 80 mm. of mercury and diastolic blood pressures of less than 60 mm. of mercury, as compared with 39 per cent of 68 untreated patients in whom postoperative shock likewise developed.

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94. Katz, F., and Mainzer, F.: Successful Grafting of Adrenal Gland in a Case of Addison's Disease, Brit. M. J. **1**:617-618 (April 26) 1941.

95. Swingle, W. W.; Hays, H. W.; Remington, J. W.; Collings, W. D., and Parkins, W. M.: The Effect of Priming Doses of Desoxycorticosterone Acetate in Preventing Circulatory Failure and Shock in Adrenalectomized Dogs, Am. J. Physiol. **132**:249-258 (Feb.) 1941.

96. Rhoads, J. E.; Wolff, W. A., and Lee, W. E.: Use of Adrenal Cortical Extract in the Treatment of Traumatic Shock of Burns, Ann. Surg. **113**:955-965 (June) 1941.

97. Besser, E. L.: Role of Adrenal Glands in Shock: Value of Desoxycorticosterone Acetate in the Prevention of Operative Shock, Arch. Surg. **43**:249-256 (Aug.) 1941.

A considerable amount of work has indicated that a close relation exists between the adrenal glands and the gonads. It has been known for some time that virilism in women, as seen in Cushing's syndrome, and pubertas praecox in children not infrequently are seen in association with tumors of the adrenal cortex. Mintz and Geist [98] have reported that the adrenal cortex is almost always involved in virilism in women. Albright and associates [99] stated that Cushing's syndrome, whatever the cause, is associated with hyperadrenocorticism.

Wintersteiner [100] reported that the urine of eunuchs and also that of ovariectomized women showed "small but definite amounts of androgenic activity." Hirschmann [101] identified the androgens excreted by ovariectomized women as androsterone and dehydroisoandrosterone. Wintersteiner expressed the belief that there was "a potential availability rather than an active functional secretion of androgens and estrogens from the adrenal cortex." He stated that this secretion did not play an important part functionally in the normal adult organism. Woolley and co-workers [102] reported that removal of the gonads of mice of either sex was followed by the development of hyperplastic adrenal cortical changes.

Emery and Gottsch [103] reported that either administration of progesterone (1 mg. or more daily) or the implantation of the pituitary glands of castrated rats will maintain adrenalectomized female rats. They expressed the belief that pituitary implantation stimulated the formation of corpora lutea, which in turn secreted increased amounts of progesterone. Estrogen not only was of no benefit in the maintenance of such rats but actually was harmful. Corey [104] confirmed the life-sustaining effects of progesterone in adrenalectomized male and pregnant or ovariectomized female rats. Progesterone could even bring

98. Mintz, N., and Geist, S. H.: Adrenocortical Syndrome: The Adrenal Cortex and Its Relation to Virilism, J. Clin. Endocrinol. **1**:316-326 (April) 1941.

99. Albright, F.; Parson, W., and Bloomberg, E.: Therapy in Cushing's Syndrome: Cushing's Syndrome Interpreted as Hyperadrenocorticism Leading to Hypergluconeogenesis; Results of Treatment with Testosterone Propionate, J. Clin. Endocrinol. **1**:375-384 (May) 1941.

100. Wintersteiner, O.: The Adrenogenital Syndrome, J. A. M. A. **116**:2679-2683 (June 14) 1941.

101. Hirschmann, H.: Steroids of the Urine of Ovariectomized Women, J. Biol. Chem. **136**:483-502 (Nov.) 1940.

102. Woolley, G.; Fekete, E., and Little, C. C.: Effect of Castration in the Dilute Brown Strain of Mice, Endocrinology **28**:341-343 (Feb.) 1941.

103. Emery, F. E., and Gottsch, L. G.: Studies on Pituitary Implants and Extracts in Adrenalectomized Rats, Endocrinology **28**:321-324 (Feb.) 1941.

104. Corey, E. L.: Comparative Effects of Progesterone and Cortico-Adrenal Extracts on Normal Adrenalectomized and Other Animals, Am. J. Physiol. **132**: 446-453 (March) 1941.

about recovery from acute insufficiency in these animals. This substance, however, did not have such beneficial effects in adrenalectomized nonpregnant female rats; the author postulated that in these animals the presence of estrogen might have prevented the effect. Smith and Smith [105] reported that among pregnant women suffering from toxemia whose hormonal balance had been found to be abnormal the administration of adrenal cortical extract had a beneficial effect, similar to that manifested by the administration of progesterone.

Since desoxycorticosterone acetate and progesterone have been shown to be closely related chemically, it might be supposed that the former would have an even greater progesterone-like effect than would the extract of the whole adrenal cortex. Indeed, in the treatment of adrenalectomized rats over a long period of adrenal insufficiency desoxycorticosterone acetate and progesterone have been reported to have similar life-sustaining effects. Selye and Dosne,[106] however, were unable to confirm these observations in experiments when acute adrenal sufficiency was present. Furthermore, Paschkis [107] has reported that desoxycorticosterone acetate had no androgenic activity in castrated rats or chicks, and Hamblen and his associates [108] reported that among 8 women, none of whom had Addison's disease, this drug neither increased the excretion of sodium pregnandiol glucuronide (the excretion product of progesterone) nor produced changes in the endometrium characteristic of a late degenerative phase of the menstrual cycle.

Stephens [109] reported on 2 patients whom he considered to have hypopituitarism and whose episodes of nausea, vomiting and low blood pressure represented, he concluded, adrenocortical insufficiency. In 1 of these patients a state of shock was precipitated by the administration of thyroid for myxedema. The symptoms of both these patients were relieved by the administration of extra sodium chloride. He advised that all patients suspected of having hypopituitarism who are to be operated on or who are to be given thyroid undergo a salt deprivation test for adrenal insufficiency as a precautionary measure.

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105. Smith, G. V., and Smith, O. W.: Effect of Hormone Administration in Pre-Eclampsia, J. Clin. Endocrinol. **1**:477-484 (June) 1941.

106. Selye, H., and Dosne, C.: Action of Desoxycorticosterone Acetate and Progesterone on Blood and Tissue Chlorides of Normal and Adrenalectomized Animals, Am. J. Physiol. **132**:522-528 (March) 1941.

107. Paschkis, K. E.: Androgenic Action of Desoxycorticosterone Acetate, Proc. Soc. Exper. Biol. & Med. **46**:336-338 (Feb.) 1941.

108. Hamblen, E. C.; Cuyler, W. K.; Pattee, C. J., and Axelson, G. J.: Studies of the Progesterone-Like Action of Desoxycorticosterone Acetate in Women, Endocrinology **28**:306-308 (Feb.) 1941.

109. Stephens, D. J.: Pituitary and Adrenocortical Insufficiency: The Use of Sodium Chloride in the Treatment of Hypopituitarism, J. Clin. Endocrinol. **1**:109-112 (Feb.) 1941.

PITUITARY BODY

Sevringhaus [110] has considered in detail the dysfunctions of the anterior lobe of the pituitary body and the treatment of them. He concluded that only two of these conditions are susceptible to successful endocrine therapy at present, namely, dysfunction involving the "growth-promoting factor" and dysfunction involving the "gonadotropic factor."

Sutton [111] reported that among 6 patients who had pellagra, polyneuritis, cheilosis or other evidence of deficiency of the vitamin B complex, improvement or recovery followed the injection of extract of the anterior lobe of the pituitary body. Cessation of this treatment resulted in relapse. In some cases of pellagra with achylia, treatment with extract of the anterior lobe of the pituitary body brought about a return of the secretion of hydrochloric acid in the stomach. Some of the patients suffering from pellagra who responded to therapy with extract of the anterior lobe of the pituitary body previously had failed to respond to the administration of nicotinic acid, riboflavin and liver substance (given parenterally) and the ingestion of an adequate diet. The author thought it possible that the hormone (or hormones) of the anterior lobe of the pituitary body was essential to utilization of the vitamin B complex.

The successful treatment of diabetes insipidus by the intramuscular administration of pitressin tannate in oil has been reported by Thorn and Stein.[112] The polyuria and polydipsia of 3 patients who received this type of therapy were controlled twenty-four to forty-eight hours by a single injection. The authors warned that excessive doses of pitressin tannate would result in retention of sodium chloride and water.

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110. Sevringhaus, E. L.: Dysfunctions of the Anterior Lobe of the Pituitary and Their Treatment, J. A. M. A. **116**:221-225 (Jan. 18) 1941.

111. Sutton, D. C.: Interrelation Between the Vitamin B Complex and the Anterior Lobe of the Pituitary Gland, South. M. J. **34**:47-51 (Jan.) 1941.

112. Thorn, G. W., and Stein, K. E.: Pitressin Tannate Therapy in Diabetes Insipidus, J. Clin. Endocrinol. **1**:680-687 (Aug.) 1941.

News and Comment

American Association of Industrial Physicians and Surgeons and American Industrial Hygiene Association.—The American Association of Industrial Physicians and Surgeons and the American Industrial Hygiene Association will hold their joint annual convention in Cincinnati April 13 to 17, 1942. Medical and hygienic problems associated with the present huge task of American industry will be presented and discussed in clinics, lectures, symposiums and scientific exhibits. The meeting will provide a five day institute for the interchange and dissemination of information on new problems, as well as for the consideration of up-to-date methods of dealing with those that are well known. The industrial physicians have taken responsibility for the program of the first two and one-half days and the hygienists for that of the remaining two and one-half days, but most of the subjects chosen for discussion will be of interest not only to physicians but to industrial engineers and executives.

Book Reviews

Body Mechanics in Health and Disease. By J. E. Goldthwait, M.D.; L. T. Brown, M.D.; L. T. Swaim, M.D.; J. G. Kuhns, M.D., and W. J. Kerr, M.D. Third edition. Price, $5. Pp. XIV + 316, with 121 illustrations. Philadelphia: J. B. Lippincott Company, 1941.

In 1922 there appeared an unobtrusive little volume called "Body Mechanics in Health and Disease." It contained only 112 pages and 31 illustrations, sold for $1.25 and was written by L. C. Thomas and J. E. Goldthwait, of Boston. It was designed primarily for directors of physical education in schools and gave common sense advice in regard to the better development of posture and correct body mechanics in children.

Apparently this booklet made no lasting impression. It soon passed into a state of innocuous desuetude, which lasted for twelve years.

In 1934 the book came to life again. It was now called "Body Mechanics in the Study and Treatment of Disease." It had grown considerably in size and was announced as the first edition of a new book rather than as the second edition of an old one. Its authors were Drs. J. E. Goldthwait, L. T. Brown, L. T. Swaim and J. G. Kuhns.

It was reviewed in a kindly manner by *The Journal of the American Medical Association* (**104**:1448 [April 20] 1935) and by the *American Journal of the Medical Sciences* (**189**:574 [April] 1935). To be sure, the authors spoke of the chronic patient and of chronic medicine—terms which *The Journal of the American Medical Association* regarded as deplorable. The book's purpose, however, was to show to its readers how modern orthopedic surgery may aid in overcoming many common disturbances of health and that to use one's body in a mechanically correct fashion is an important adjunct to well-being. The book fulfilled this purpose adequately and had a reasonable degree of success.

A new edition was printed in 1937, and now still a fresher one is obtainable. The chief differences between the latest model and the one of 1934 is that W. J. Kerr has appended a chapter on the relation of the heart and circulation to body mechanics, that the title has reverted to the one of 1922 and that the material throughout is better arranged.

From the viewpoint of bookmaking the 1941 model is excellent. While it is 35 pages larger than it was seven years ago, it weighs a few ounces less, so that it has a streamlined appearance. The paper is a little finer; the type is handsome, and the illustrations are clear and ingenious. The book continues to reveal to its readers how modern orthopedic surgery may aid in overcoming many common disturbances of health and that to use one's body in a mechanically correct fashion is an important adjunct to well-being. No doubt once again it will achieve a reasonable degree of success.

The Blood Bank and the Technique and Therapeutics of Transfusions. By R. A. Kilduffe, M.D., Director of Laboratories, Atlantic City, N. J., and M. DeBakey, M.D., Assistant Professor of Surgery, Tulane University of Louisiana. Price, $7.50. Pp. 558, with 214 illustrations and 1 colored plate. St. Louis: C. V. Mosby Company, 1942.

This book represents a timely effort which must have been accomplished under great pressure. More than twenty-eight hundred articles are referred to in the bibliography, which gives an idea of the huge literature that required analysis in order to put together a satisfactory monograph on the many problems of blood transfusion.

The subject matter of the volume is well organized. A chapter on the history of transfusion precedes fifteen pertinent chapters on this general topic, including

how to build a satisfactory blood bank. The book ends appropriately with accounts of plasma transfusion and the preparation and preservation of wet or dry plasma and two concluding chapters on the technic of transfusion and its complications. The illustrations do much to clarify procedures which may appear complicated. The literary style employed is easy to follow. Everything about the volume is done handsomely. In brief, this is a book which should be widely read. It is a fine piece of work.

The only fault to be found with it is that nowadays the blood transfusion and blood bank business is so booming that new methods and viewpoints concerning it are being developed with astonishing rapidity. Fresh ideas crop up constantly, and a technic usable today is obsolete tomorrow. This particular book brings one down to July 1941 and already is several months out of date. The authors, no doubt, have met this objection and have a second edition under way through which to add the latest ideas on transfusion and blood collection in these perilous times when the proper use of blood or blood substitutes can save so many lives.

Die Ursachen der Entstehung des Kropfes. By J. U. Duerst, M.D., Professor of Hygiene, Faculty of Veterinary Medicine, University of Berne, Switzerland. Price, 24 francs. Pp. 539, with 82 illustrations. Berne: Medizinischer Verlag Hans Huber, 1941.

The author has succeeded in assembling a compendium of information about goiter, which commences with a detailed study of the comparative anatomy of the thyroid gland and ends with suggestions as to how various forms of goiter may be prevented. Obviously, it is the work of a careful student who is much interested in his subject.

Certain of the chapters appear of theoretic rather than practical interest. On the other hand, the volume does not pretend to be an ordinary textbook but rather is a general discussion of the thyroid from such varied points of view as how this gland is influenced by such factors as hibernation, climate, food, other endocrine glands and inheritance.

The book is well printed and illustrated. An excellent bibliography at the end includes most of the recent literature on the thyroid and the thymus. It is a good book for reference.

Electrocardiography. By Louis N. Katz. Price, $10. Pp. 580, with 402 engravings. Philadelphia: Lea & Febiger, 1941.

A large number of books on electrocardiography of varying excellence have appeared during the past few years. The present work, as one might expect from the author's qualifications as a cardiac physiologist, deals with the subject in a scholarly way and in great detail. The various features of tracings, normal and abnormal, are analyzed and discussed meticulously. Indeed, in part it makes rather heavy reading because of the very detail. The book is handsomely got up and profusely illustrated with many reproductions of electrocardiograms, apparatus, diagrams, etc. The sections on theory discuss not only the author's views but the subject in general.

Stethoscopic Heart Records. By G. D. Geckeler, M.D. A set of 7 phonograph records. New York: The Columbia Recording Corporation, 1941.

These phonograph records contain an assortment of normal and abnormal heart sounds. Preceding each illustration, a voice explains the sound which is to be heard and its significance. Normal heart tones, arrhythmias, reduplications and many varieties of murmurs are reproduced. Although it is possible to listen with any degree of amplification, the instructions advise that the listener insert the ear pieces of his stethoscope in his ears and reduce the volume of the spoken voice to a point where it can just be heard distinctly. Unless this is carried out, faithful reproduction cannot be assured. This feature limits the use for large classroom instruction. The records should, however, be of some value to small study groups or to small sections in physical diagnosis.